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The Archives of Internal Medicine

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HEART-BLOCK

II. TRANSIENT COMPLETE HEART-BLOCK WITH NUMEROUS STOKES-ADAMS ATTACKS *

FRANK N. WILSON, M.D.
AND
G. CANBY ROBINSON, M.D.
ST. LOUIS

Although syncopal attacks are fairly common in cases of complete heart-block, they do not, as a rule, occur with sufficient frequency in any given case to allow the cardiac mechanism during an attack to be graphically recorded. Polygrams have been obtained during such attacks by Lewis,[1] and Williams[2] has obtained an electrocardiogram during an attack in one instance. The following case is of interest because electrocardiographic records were obtained during several Stokes-Adams attacks, and also as an example of transient complete heart-block.

REPORT OF CASE

History.—Mrs. N. M., an American housewife, aged 48, entered the Barnes Hospital, May 10, 1917, on the advice of her family physician, Dr. George Park. She complained of fainting spells, vomiting and pain in the epigastrium and back. The family history was unimportant. She had had measles, mumps and a number of attacks of severe sore throat during childhood; but had been otherwise well until about ten years before, when she began to suffer from palpitation of the heart and slight dyspnea on exertion, both of which symptoms had continued up to the onset of the illness for which she entered the hospital. She had never had a severe attack of cardiac decompensation. She had had several attacks of severe pain in the epigastrium and back with fever and vomiting, and one such attack was accompanied by jaundice.

Present Illness.—About April 18, 1917, she became ill with pain in the epigastrium and back similar to that which she had experienced in previous attacks. At this time she also had nausea and vomiting and some fever. Her general condition remained about the same until the night of May 9. At about midnight of this date she became nauseated and asked for water. Her husband went to procure this, and when he returned he found her unconscious. Her pulse was weak and irregular. A dash of cold water in the face revived her. During the

* Submitted for publication Sept. 1, 1917.

* From the Department of Internal Medicine, Washington University Medical School.

1. Lewis, T.: Lectures on the Heart, New York, Paul B. Hoeber Company, 1915.

2. Williams: Personal communication.

course of the night she had ten or twelve such attacks, and several more occurred during the next forenoon. About 1 p. m., May 10, 1917, she was brought to the hospital. She was then having a syncopal attack every one or two minutes. These attacks were described by the intern in charge about as follows: Each attack was preceded by a cessation of the heart sounds and of the pulse, which did not return for from three to ten seconds. Just before the pulse returned, after the longer pauses, the patient became cyanotic and very dyspneic, the eyes turned upward and she became unconscious. At the end of the longer attacks there was some twitching of the extremities and occasionally of the whole body. The heart sounds and the pulse then returnd, the patient quickly regained consciousness and the cyanosis and dyspnea disappeared.

Physical Examination.—Aside from these attacks the examination of the patient revealed little that was abnormal. The cardiac dulness extended 3 cm. to the right and 10 cm. to the left of the midline. On auscultation there was a systolic murmur, heard best along the left border of the sternum, but heard distinctly at the apex and transmitted into the axilla. There was no edema of the ankles, ascites or hydrothorax. The liver extended 3 cm. below the costal margin and there was slight general abdominal tenderness. The temperature reached 100.5 F. on the day of admission, but was normal thereafter. The remainder of the physical examination and the laboratory examinations, including the Wassermann reaction, were negative.

GENERAL SURVEY OF THE GRAPHIC RECORDS

A general survey of the graphic records and the course of the patient's illness will be given first, after which the records will be described in detail. The electrocardiograms taken May 10 shortly after the patient entered the hospital and while she was having syncopal attacks, revealed the presence of complete auriculo-ventricular dissociation with frequent periods of ventricular standstill lasting from seven to eleven seconds, and corresponding to the syncopal attacks. About one-half hour later these periods of ventricular standstill began to be interrupted in the electrocardiograms by abnormal ventricular complexes, and at about the same time the syncopal attacks ceased. During all of this time the ventricular rate between periods of ventricular standstill was approximately 90 per minute, while the auricles beat uninterruptedly at a rate of about 120 per minute. About one hour after the first curves were taken, however, single normal ventricular complexes began to interrupt the periods of ventricular standstill and these periods became comparatively short. One-half hour later the short periods of high ventricular rate with complete dissociation had disappeared and a partial heart-block of high grade was present.

On the following day, May 11, complete dissociation returned for a time, but there were no periods of ventricular standstill and the complete dissociation quickly gave place to a 2:1 block. The partial block then became gradually less marked until May 14, when the only sign of defective conduction which remained was a prolongation of the P-R interval which measured 0.31 second. Thereafter, the improve-

ment in conduction was less rapid, but by May 25 the P-R interval had decreased to 0.20 second. During this time there was also a rapid improvement in the patient's general clinical condition.

The general picture, then, was one of complete dissociation with a rapid idioventricular rate and ventricular standstill causing Stokes-Adams syndrome. This was followed by improvement associated with a rapid decrease in the grade of the heart-block.

DETAILED DESCRIPTION OF THE GRAPHIC RECORDS

Figure 1 is an example of the electrocardiograms that were obtained at about 2 p. m. May 10, when the patient was having frequent syncopal attacks. It begins with a period of complete A-V dissociation during which the ventricular rate is 89.3 and the auricular rate 120 per minute. This period of complete dissociation is followed by a period of ventricular standstill lasting 9.06 seconds. During this period there is a gradual acceleration of the auricular rate, probably due to anemia of the vagus center, or possibly to the fall of blood pressure. The period of ventricular standstill is terminated by a period of complete dissociation exactly like that at the beginning of the figure. From the examination of a number of tracings similar to this one it became apparent that there was a fairly constant time interval between the first ventricular complex following a period of ventricular standstill and an auricular beat preceding it. This relationship was sufficiently constant to warrant the conclusion that the periods of ventricular standstill were terminated by an effective impulse passing from the auricles to the ventricles.

Figure 2 is an example of the electrocardiograms obtained about 3:00 p. m., May 10, at about the time that the syncopal attacks ceased. It is very similar to Figure 1, except that in it the long period of ventricular standstill was interrupted by the occurrence of ventricular contractions yielding complexes suggesting stimulus production within the left ventricle. The relationship of the first normal ventricular complex following the long pause to the preceding P wave is slightly but not markedly different from that seen in the previous figure. It will be noted in Figure 2 as well as in the other figures that the ventricular complexes following long periods of ventricular standstill differ somewhat in form from the others. This difference is partly due to the prolongation of the R-T time and is probably analogous to the changes in the form of the ventricular complex which occur as a result of changes in heart rate.

Records obtained shortly after Figure 2, show in addition to the abnormal ventricular complexes single normal ventricular complexes interrupting the period of ventricular standstill. These normal beats

bear the same relationship to the previous auricular beat as do the first ventricular beats after the long pauses.

Figure 3 is an example of the curves obtained shortly after Figure 2. The abnormal ventricular complexes no longer occur, but single normal ventricular complexes occur during the pauses at the rate of 1 for every 4 auricular beats, each ventricular complex bearing the same relationship to the preceding P wave as the first ventricular complex of a group. During the pauses 4:1 block is present, while during the periods of rapid ventricular rate there is complete dissociation.

Figure 4 is an example of the electrocardiograms obtained about 4:05 p. m., May 10. The groups of rapidly recurring ventricular beats no longer occur, and partial heart-block of high but somewhat mixed grade is now continuously present. Records obtained shortly after that shown in Figure 4 indicated a lower grade of partial block.

Figure 5 is an example of the curves obtained between 10:30 and 11 a. m., May 11. This figure shows a return of complete dissociation. The ventricular rate, however, is now only 66 per minute, instead of 90 per minute as on the previous day. Moreover, there are no periods of ventricular standstill. At this time the patient was given one-fiftieth grain of atropin sulphate hypodermically.

Figure 6 was obtained seven minutes after the atropin was injected. We see in this figure a 2:1 block with a ventricular rate of 56 as compared with 66 in the previous figure. This 2:1 block continued without change for the next hour. In view of the fact that it came on so soon after the administration of the atropin and that there was no change in the block during the next hour, it seems unlikely that the atropin was responsible for the disappearance of the complete block seen in the previous figure in favor of partial block. On the other hand we believe that this was due to the slowing of the idioventricular rate.

On the following day, May 12, the partial block was of still lower grade, a mixture of 3:2, and 4:3 rhythm.

Figure 7 was taken at 10:45 a. m., May 14, four days after admission. Each auricular beat now produces a ventricular response, and the only sign of defective conduction is the prolongation of the P-R interval which measures from 0.310 to 0.315 second.

DISCUSSION

In discussing the cause of the periods of ventricular standstill and consequently of the syncopal attacks, we may first examine the tracings in the light of previous experience. Such periods of ventricular standstill are known to occur when complete heart-block is suddenly produced in the experimental animal, and also when a high grade of

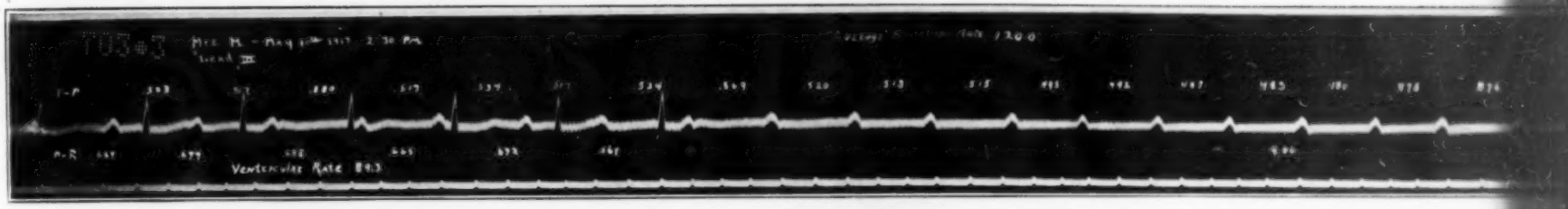


Fig. 1.—May 10, 2:30 p. m. Record obtained during one of the attacks of syncope, showi

Fig. 2.—May 10, 3 p. m. The periods of ventricular standstill were interrupted by abnormal ventric

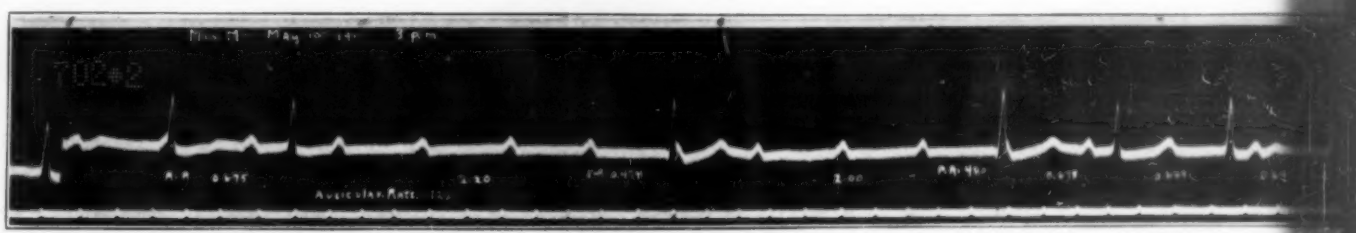
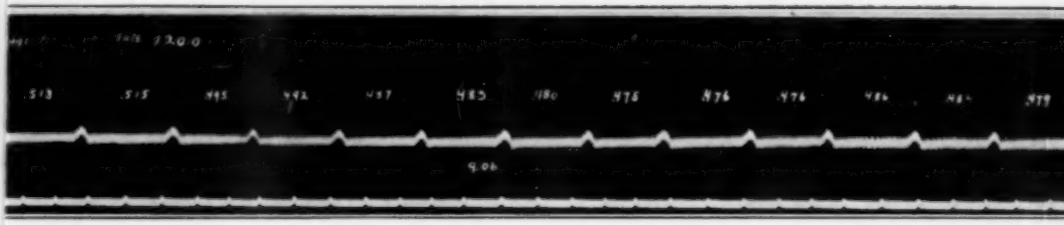
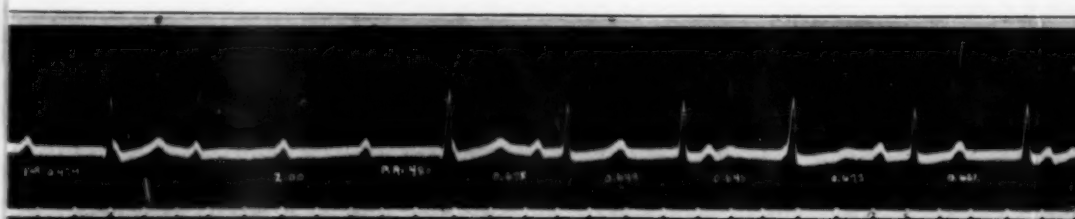


Fig. 3.—May 10, 3:10 p. m. The abnormal ventricular complexes no longer appear, but partial heart-block; 4 to 1



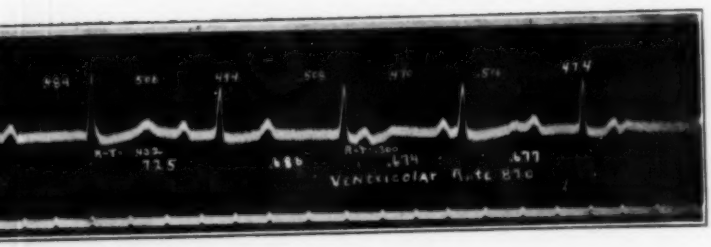
y 10, 2:30 p. m. Record obtained during one of the attacks of syncope, showing ventricular standstill of 9.06 seco

m. The periods of ventricular standstill were interrupted by abnormal ventricular complexes. Syncope did not occ



abnormal ventricular complexes no longer appear, but partial heart-block; 4 to 1 rhythm occurs between periods of

seconds.



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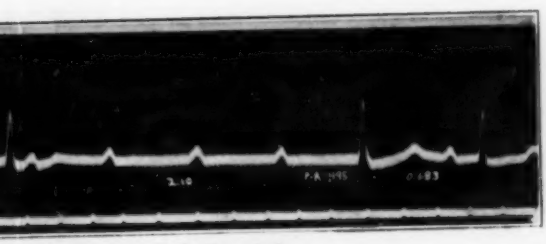
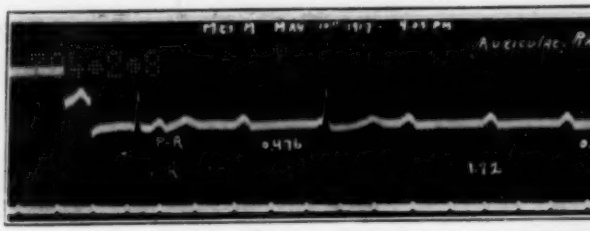


ods of complete A-V dissociation.



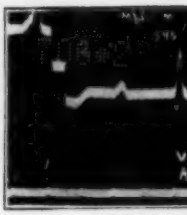


Fig. 5.—May 11,

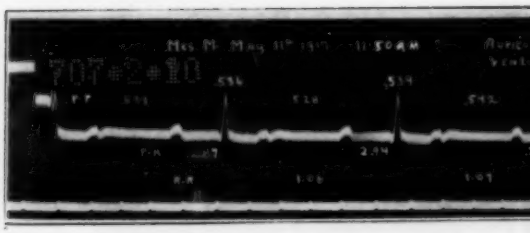


Fig. 6.—May 11. 11:50 a. m. P

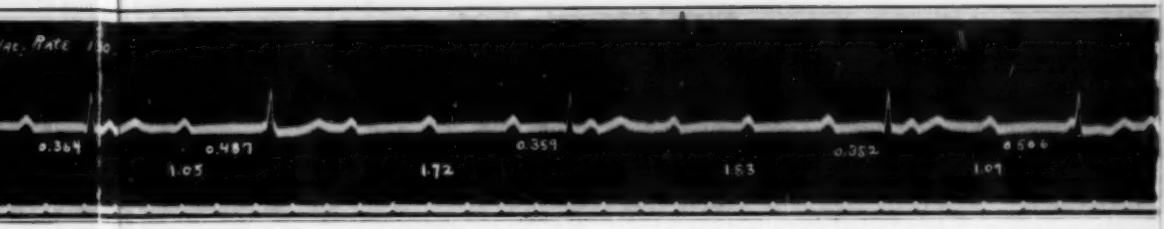
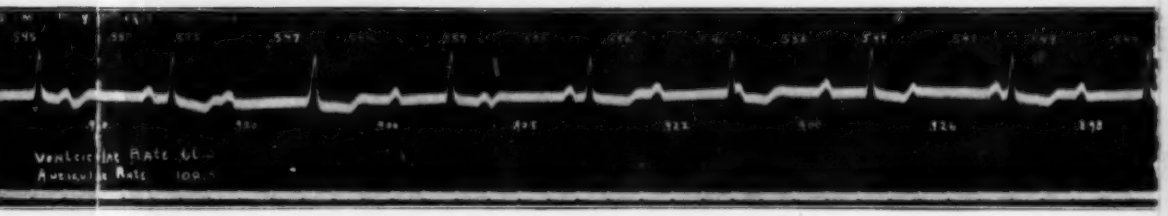
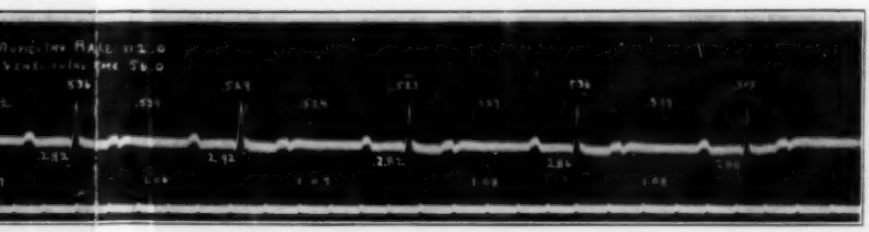


Fig. 4.—May 10, 4:05 p. m. Complete A-V dissociation no longer occurs. It is replaced by partial heart-block of vary

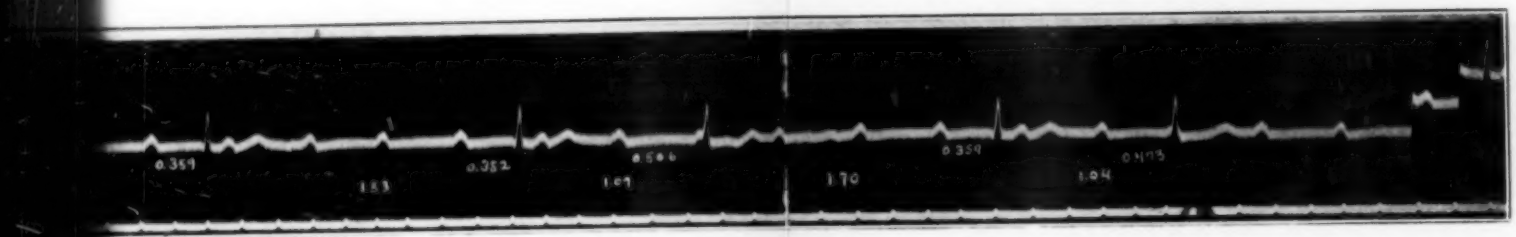


y 11, 10:30 a. m. Complete A-V dissociation is again present. The idioventricular rate is now 66 per minute instead of 90,



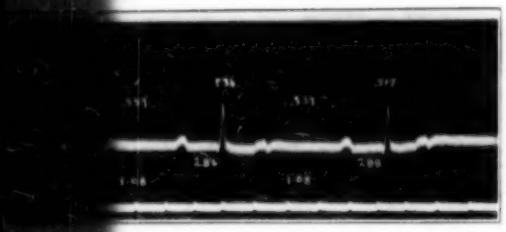
. Partial heart-block, 2:1 rhythm. Ventricular rate 56 per minute.

Fig. 7.—May 12, 1



dissociation no longer occurs. It is replaced by partial heart-block of varying grade.

gata present. The idioventricular rate is now 66 per minute instead of 90, as was present the day before.



te 56 per minute.

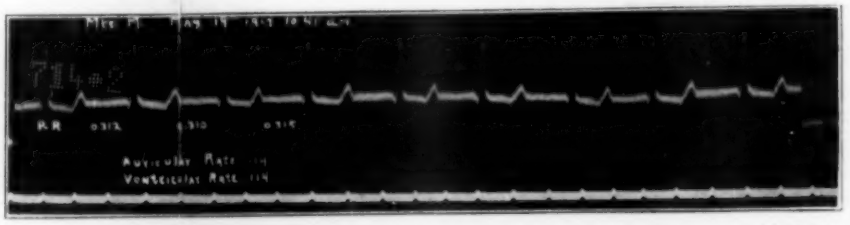


Fig. 7.—May 12, 10: 45 a. m. Delay in A-V conduction, but no auricular beats are blocked.

partial block suddenly becomes complete in man. In these instances ventricular stoppage is due, according to Erlanger and Hirschfelder,[3] to the slow development of the idioventricular rhythm. In our case, however, none of the above conditions were present; we are dealing with very numerous periods of ventricular standstill occurring while complete block was continuously present. Moreover, the ventricles did not develop their rhythm gradually at the end of a period of standstill but started in at full speed. In looking for unusual features which might explain the ventricular stoppage the attention is attracted by the unusually rapid idioventricular rate, which was about three times as fast as the usual idioventricular rate seen in complete heart-block. This seems to offer an analogy. The ventricular tachycardia in this case bears certain resemblances to a well recognized type of tachycardia, namely, paroxysmal tachycardia, which is characterized by the suddenness of its termination. In some cases of tachycardia there is perhaps a causal relationship between the successive beats of the paroxysm; each beat seems to be necessary for the production of the following beat. If for any reason any beat of the series fails to occur, the tachycardia comes to an end. Somewhat the same mechanism may be discerned during the periods of idioventricular tachycardia which occurred in our patient. Each period stopped suddenly without ascertainable cause.

The mechanism by which the ventricular stoppage was terminated became evident when a number of records were examined. It was found that the first ventricular beat following the long pauses bore a fairly constant relationship to a preceding auricular beat, indicating that these beats were sequential and that the ventricular stoppage was terminated because an impulse from the auricles reached the ventricles. The auricular impulse did not stimulate the ventricles, however, until the ventricular stoppage had continued sufficiently long to produce the conditions in the heart which were necessary for the effective passage of the impulse. In the later records, when conduction was somewhat improved, the periods of standstill were shorter.

It seems likely, therefore, that the ventricular stoppage was at least partly dependent on the abnormal character of the ventricular rhythm during the periods of ventricular tachycardia. The length of the periods of ventricular standstill was apparently determined by the time required for sufficient improvement in the auriculoventricular conductivity to allow an auricular stimulus to reach the ventricles; for, as the degree of block diminished the periods of ventricular standstill became shorter. The periods of standstill were apparently never long

3. Erlanger and Hirschfelder: Am. Jour. Physiol., 1905-1906, **15**, 153.

enough to allow the usual slow idioventricular rhythm to develop. Three factors, then, took part in the production of the syncopal attacks: the abnormal character of the ventricular rhythm, the high grade of heart-block, and the slow development of the idioventricular rhythm.

The cessation of the syncopal attacks was apparently due to the occurrence of ventricular contractions arising in the left ventricle during the long ventricular pauses. These beats, although they did not always occur after the elapse of exactly the same period of time following the occurrence of ventricular stoppage, were probably due to an impulse generated in one of the lower ventricular centers. Had these beats failed to occur, however, the attacks would soon have ceased because of the rapid improvement in A-V conduction and the gradual disappearance of the tendency to ventricular tachycardia which are shown by the later records of May 10.

The occurrence of a period of complete dissociation, May 11, appears to have been due to the recurrence of a ventricular rhythm of high rate. This rhythm may or may not have been of the same character as that previously observed. The ventricular rate was considerably slower and there was apparently no tendency to ventricular stoppage at this time. This ventricular tachycardia disappeared rather suddenly after, but probably not as a result of, the administration of atropin, giving place to a 2:1 rhythm. During the 2:1 rhythm the ventricular rate was considerably slower and it is possible that it was the rapid ventricular rate and not the condition of the junctional tissues alone which was responsible for the previous complete dissociation.

Two explanations may be given for the occurrence of such a phenomenon. The rapidly recurring ventricular beats may in some way depress the conductivity of the His bundle. This idea is supported by the occurrence of prolonged P-R intervals after interpolated ventricular extrasystoles. Erlanger,[4] however, has suggested a different explanation. His view may be expressed as follows: The irritability of the ventricles during the refractory period is zero; following the refractory phase the irritability of the ventricles increases according to a definite curve. The height to which the curve of irritability rises depends on the form of the curve and on the duration of ventricular diastole. The value of the threshold stimulus depends at any time, therefore, on the time which has elapsed since the previous ventricular beat and the rate of recovery of the ventricles. When, because of the high rhythmicity of some ventricular center, the ventricles are driven at a rapid rate, the general ventricular irritability never reaches a high level. It is conceivable that in such instances the stimuli from the auricles may fail to be effective on reaching the ventricles because they lie below the

4. Erlanger: Personal communication.

threshold value. When, as in the present case, the ventricular rate is relatively slow when compared with other types of tachycardia, this explanation is inadequate unless we further assume that the strength of the auricular stimuli reaching the ventricles is diminished by the defective A-V conduction, or that the increase in ventricular irritability is much less rapid than is usually the case. So far as we know, there is no exact experimental evidence bearing on this problem.

It remains to inquire into the etiology of the heart-block in our patient. The rapidity with which the block cleared up suggests that it was not due to some destructive lesion of the A-V bundle, but to some toxic or acute inflammatory process. The patient had received small doses of digitalis (5 drops of a proprietary preparation) for a period of about one week before entering the hospital; but it seemed unlikely that this small amount of the drug could have been responsible for the block unless the patient was especially susceptible to the digitalis bodies. To decide this point the tincture of digitalis was administered to the patient for a considerable period, beginning about two weeks after she entered the hospital. No marked changes in conduction were observed. The patient's history and the slight fever on the day of admission to the hospital indicate that she had recently had an acute infection, and it is possible that this was in some way responsible for the lesion which caused the block. The presence of an old endocarditis and possibly a chronic myocarditis indicated by the history and the presence of mitral regurgitation may have been a contributory factor.

SUMMARY

A case of transient complete heart-block is reported. When first observed the patient was having a great many syncopal attacks and the cardiac mechanism during some of these was recorded electrocardiographically. The attacks were caused by ventricular standstill lasting from seven to eleven seconds. The patient made a rapid clinical recovery, and at the same time there was a rapid decrease in the grade of block. The cause of the syncopal attacks and the etiology of the heart-block are discussed.

THE ENDOCRINE ORIGIN OF MUSCULAR DYSTROPHY *

N. W. JANNEY, M.D., S. P. GOODHART, M.D.
AND
V. I. ISAACSON, B.S.
NEW YORK

SCOPE OF THE PRESENT COMMUNICATION

Certain clinical and pathologic observations suggest that muscular dystrophy may originate as a result of dysfunction of the endocrine organs. Such a view requires, however, the support of evidence of metabolic nature before it can be regarded as acceptable. In the present investigation the metabolism in nine cases of muscular dystrophy was accordingly studied. In addition to certain disturbances in the creatinin-creatin metabolism, there was observed constant hypoglycemia and impaired utilization of carbohydrate. The metabolic picture presented is essentially the same as that recorded in the diseases of unquestionable endocrine origin (myxedema, hypopituitarism and Addison's disease) and after experimental removal of the thyroid or adrenal glands in animals. In view of these metabolic findings, also the clinical as well as pathologic, it seems justifiable to regard muscular dystrophy a result of dysfunction of the ductless glands.

CLINICAL MATERIAL

This was selected from the neurologic wards of the Montefiore Hospital, and consisted of a representative series of muscular dystrophy cases, including both light and severe, in children and adults. Our patients well exemplify the fact that muscular dystrophy is a distinctly familial disease, for eight of our nine patients gave such a history. The greater tendency of males to become affected is shown by the fact that eight patients were men or boys. Practically all gave evidence of trophic changes in the nails, skin, hair, etc. A peculiar distribution of hairy areas was observed in three cases. Pigment deposits, osseous changes, etc., were also found.

Roentgenologic studies were made in each instance. The results are very instructive. Aside from Case 1 in which the findings were negative, the entire series showed rarefaction of the skull and long bones, in some cases underdevelopment, in two cases pineal shadows.

* Submitted for publication Sept. 18, 1917.
* From the Montefiore Hospital.

The osseous system is evidently almost as frequently affected as is the muscular, as will be observed by reference to the accompanying roentgenograms. Case 9 showed acromegalic changes. Abstracts of the patients' histories follow. The cases are arranged throughout the article in the order of their severity.

REPORT OF CASES

CASE 1.—Joseph G., a boy, aged 11 years, had one sister who was affected with muscular dystrophy. He was operated on four years previously for cataracts of both eyes. His present illness began at the fourth year with distinct progressive weakness in all the muscles of the body. There is at present general muscular wasting and weakness with the exception of the calf muscles

Fig. 1 (Case 1).—Showing general muscular wasting, "winged" scapulae, and the characteristic manner of rising from recumbent position.

which are in a condition of pseudohypertrophy. When lying on the floor the patient assumes the erect position in a characteristic manner by rising on one knee, extending the other leg, pulling himself up on that and then dragging up the other leg (Fig. 1). There is a myotonic reaction in the tongue, thenar and hypothenar eminences and the deep reflexes are but feebly elicited. When walking the patient has a characteristic steppage gait. On appropriate movements there are typical winged scapulæ. The facies is of the myopathic type and there is very little fatty tissue. There are hirsutes on the extensive surface of the upper extremities just above and below the elbow. Marked cyanosis is present in the peripheral portions of all four extremities which is only slightly influenced by posture, the hands remaining distinctly cyanosed even when elevated. The Wassermann reaction is negative.

The roentgenographic examination of the skull and long bones was essentially negative.

CASE 2.—H. S., a woman, aged 43. One brother died at the forty-fifth year of progressive muscular dystrophy. The onset of the disease began in her thirty-eighth year with weakness in the lower extremities, and upper extremities in lesser degree. Motor paresis in neck muscles developed later. Present status: Facies characteristic of primary myopathy (Fig. 2); motor power markedly diminished; intense cyanosis of feet; volume of musculature is lost throughout the body, with far greater relative diminution of function; gait slow and hesitating, with broad base; wasting of muscles of neck and shoulders; sternocleido-

Fig. 2 (Case 2).—Facies characteristic of primary myopathy.

mastoids atrophic; myotonic reaction in muscles of tongue and right thenar and hypothenar eminences. The patient is unable to raise herself on the chair without assistance, and she has a low monotonous speech.

The roentgenographic examination shows small spots of bone absorption scattered throughout the upper portion of the cranium. There is a faint shadow, about 5 by 7 mm. situated slightly above and 3.5 cm. posterior to the tip of the posterior clinoid process. This shadow suggests the pineal gland.

CASE 3.—N. B., a man, aged 42, has two brothers known to have muscular dystrophy. The patient lived under unhygienic conditions, his work exposing him to metallic dust of lead, brass, antimony, etc. The onset began at the twenty-sixth year, was gradual, with progressive weakness in right arm, extending to left, then involving both lower extremities. There is marked exoph-

thalmos and dilated pupils (Fig. 3). The patient cannot assume a sitting posture but maintains it when assisted. The head is flexed and rotated to the right. There is marked atrophy of the sternocleidomastoids, trapezii and muscles of the forearms. The deep reflexes are absent (knee jerks diminished). The characteristics in this case are contrasted pseudohypertrophy and weakness of function of the calf muscles. The muscle tissue seems to be replaced almost entirely by fat. The Wassermann reaction is negative.

The roentgenographic examination shows very marked bone rarefaction in the skull, evidently in the tabula interna, simulating strongly the convolutions of the brain. The extremities show moderate diffuse bone rarefaction, somewhat more marked in the lower. In both tibiae there is evidence of very advanced localized bone absorption running in the form of two narrow strips throughout the upper half of the diaphysis, suggesting cavity formation (Fig. 4).

Fig. 3 (Case 3).—Muscular dystrophy with marked exophthalmos.

CASE 4.—L. S., a man aged 48, has two brothers who are affected with primary myopathy. At the thirtieth year in our patient weakness began in both upper and lower extremities (Fig. 5). He is able to move about only in a wheelchair, and has difficulty in assuming a sitting position. There is flexion of both thighs and knees and contraction of the hamstring muscles. Extension of legs is limited to 130 degrees. His body is of wasp-like contour, facies myopathic, and the calf muscles are weak with the characteristic sclerotic feel. Pseudohypertrophy is present. There is marked wasting of the general musculature. The deep reflexes cannot be elicited because of atrophy. Electrical examination shows quantitative changes in the affected muscles. The skin is cold and clammy, the feet cold and cyanotic and there are trophic changes in the nails. The pulse is slow and of low tension.

Roentgenographic examination shows several small irregular spots of bone absorption scattered throughout the parietals and frontals (Fig. 6). There is an irregular shadow, about 0.5 to 1 cm. on the level of and 4 cm. posterior to the tip of the posterior clinoid process (pineal body?). Evidence of bone

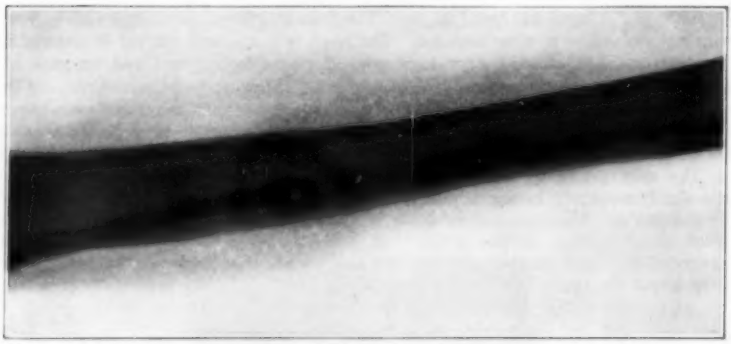


Fig. 4 (Case 3).—Evidence of localized bone absorption in the tibia. The narrow strips of bone throughout the upper half of the diaphysis suggest cavity formation.

Fig. 5 (Case 4).—General muscular dystrophy with pseudohypertrophy of calf muscles.

absorption of the posterior clinoid process is present; the sella turcica is not enlarged, and there is marked, diffuse bone atrophy in the upper extremities. In some places differentiation between compacta and spongiosa has entirely disappeared. There is a moderate amount of diffuse atrophy of all bones of the lower extremity, including tarsal bones.

CASE 5.—L. K., aged 19, has two brothers who are affected with progressive muscular dystrophy. There is an extra digit on all four extremities (congenital deformity). The onset began at the third year with progressive weakness, in the order named, of the lower extremities, upper, back, and facial musculature (Fig. 7). The calf muscles show the usual pseudohypertrophy with

Fig. 6 (Case 4).—Small irregular spots of bone absorption throughout the parietal and frontal bones. The irregular shadow toward which the arrow points at the anatomic location of the pineal body would seem to indicate an enlarged organ.

the characteristic sclerotic feel. The whole skeletal structure appears stunted; the long bones between the knees and the ankle are abnormally short, and there is a peculiar distribution of the hirsutes, the individual hairs being abnormally long, especially about the groins and thighs anteriorly.

The roentgenographic examination shows underdevelopment of the long bones and absorption of osseous tissue.

CASE 6.—H. B., aged 18 years. His father is an epileptic, and he has two brothers affected with muscular dystrophy. One maternal aunt is insane.

The onset began at the fifth year with generalized muscular weakness and slowly progressive wasting. The calf musccles show typical pseudohypertrophy (Fig. 8), and the orbicularis oris and palpebrarum muscles are atrophic. The trunk deformities are in large part due to muscle wasting. The hair is strikingly long and abnormally distributed; scalp hair very dry and brittle and there are trophic ulcers on the fingers and toes.

The roentgenographic examination shows marked, diffuse rarefaction of all bones examined. They are abnormally thin and underdeveloped (Fig. 9).

CASE 7.—James G., a boy, aged 15. There is profound muscular weakness with contractures involving almost the entire musculature of the limbs and trunk. The sternocleidomastoids are atrophied and there is extreme distortion

Fig. 7 (Case 5).—Whole skeletal structure appears to be stunted; pseudohypertrophy of calf muscles; long bones between knees and ankles abnormally short; peculiar distribution of hirsutes.

of the trunk (Fig. 10). This case represents an advanced muscular degeneration. The facial muscles on both sides are involved in the typical myopathic loss of function on effort. The exophthalmos is emphasized by the partial wasting of the orbiculares palpebrarum. There is marked dryness of the skin on the abdomen and a deposition of brown pigment. The teeth are wide apart, and there is macroglossia.

The roentgenographic examination shows marked underdevelopment and rarefaction of all bones examined, most advanced in the carpus and tarsus.

CASE 8.—M. E., aged 19 years, has one brother affected with muscular dystrophy. At the third year the patient's manner of gaining the erect position typical of muscular dystrophy was observed. He was never able to run and

climb stairs. There is marked wasting of all muscles of the body and contractures in the hamstrings and calf muscles (Fig. 11). The enlargement of the calf muscles and the peculiar sclerotic feel are in contrast to the marked general atrophy elsewhere. The skin is peculiarly dry, with diffuse areas of brownish pigmentation and a prolific, long hairy growth about the pelvis and thighs. The cyanosis of the lower extremities in the distal portions is marked and there is a tendency of the soft parts to ulceration.

The roentgenographic examination shows atrophy of all bones examined. The lower portions of ulnae and radii are abnormally thin from underdevelopment.

Fig. 8 (Case 6).—Deformities of trunk due in large part to muscle wasting; pseudohypertrophy of calf muscles; atrophic condition of orbicularis oris and palpebrarum muscles; abnormal distribution of hair; trophic ulcers on fingers and toes.

Case 9.—I. R., boy, aged 14 years, gives a family history which contains no element relevant to the patient's condition. The initial symptoms bearing on the development of the muscular dystrophy date from the boy's third year. The patient gave the history of gradual weakness beginning in the lower extremities, progressively involving girdle, facial and shoulder musculature (Fig. 12). Pseudohypertrophy and atrophy have finally reached a very high degree. There is also, in part secondary to the marked involvement of the trunk muscles, extensive kyphoscoliosis from sixth dorsal to midsacral region. The general massive bony contour of the head and face, and especially the marked prognathic lower maxilla, are decidedly of the acromegalic cast. The sexual development, in contradistinction to the other cases reported, shows abnormally advanced maturity of growth (Fig. 13). There is marked macro-

Fig. 9 (Case 6).—Showing marked rarefaction and underdevelopment in the bones of the hand and forearm. This diffuse rarefaction was present in all of the bones examined.

Fig. 10 (Case 7).—Profound muscular weakness with contractures involving almost the entire musculature of the limbs and trunk; extreme distortion of trunk; typical myopathic loss of function of facial muscles, etc.

Fig. 11 (Case 8).—Marked wasting of all the muscles of the body and contractures in the hamstrings and calf muscles.

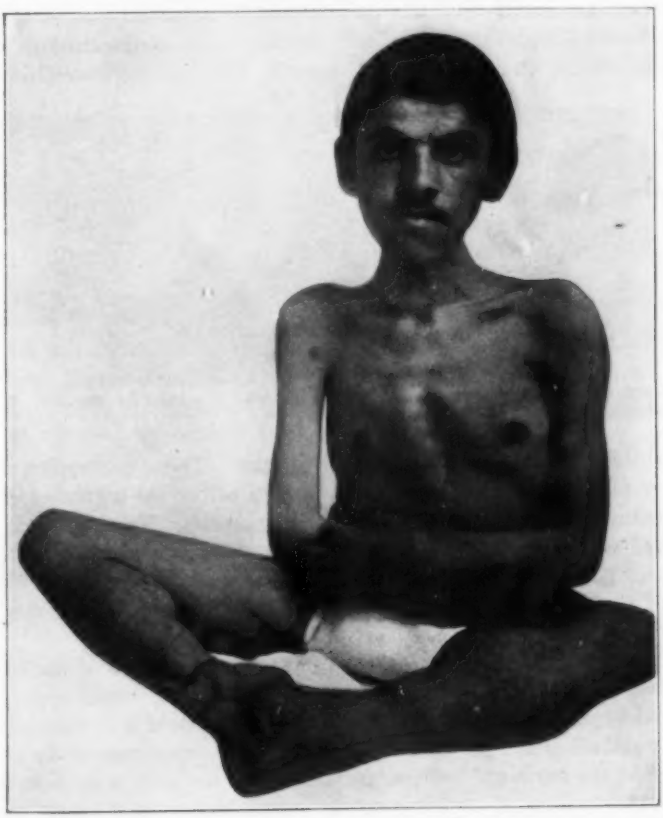


Fig. 12 (Case 9).—Marked involvement of trunk muscles; extensive kyphoscoliosis from sixth dorsal to midsacral region; general massive contour of head and face; prognathic lower maxilla; decided acromegalic cast; excessive growth of hair over body.

glossia, the tongue in protrusion being really huge (Fig. 14). There is excessive hair growth over the entire body.

Roentgenographic study of the skeleton structure examined, shows the usual underdevelopment of the long bones. Those of the skull, especially the lower jaw, present markedly acromegalic features.

METHODS OF INVESTIGATION

In general the methods employed were those described in previous articles by one of us. The advantages of a metabolism ward were utilized in this study. The cases were segregated under constant supervision in separate rooms, and cared for by night and day nurses trained in metabolism studies. A special diet kitchen was used. The diet was creatin-creatinin free, was kept uniform during the experimental periods, and in all cases was weighed. Representative articles of food used were bread, butter, eggs, milk, potatoes, rice, pears, custard, sweet corn, orange, and lettuce, the amounts taken varying somewhat with

Fig. 13 (Case 9).—The underdevelopment of the long bones with contrasted acromegalia of the bones of the skull, especially the inferior maxilla, is very marked in this case.

the clinical condition and age of the patients. Those undergoing study were placed on the diet four to seven days before the beginning of the experimental period, as recorded in the protocols. The urine was collected in twenty-four-hour periods with proper precautions. In the cases of three patients who were helpless cripples it was found impossible sharply to demarcate the twenty-four-hour periods, and this fact is noted in the protocols.

The metabolic studies consisted in the determination of the endogenous creatinin-creatin metabolism, total nitrogen, blood sugar and blood sugar tolerance curves. It is fully recognized that these phases of metabolism are partial only and should be supplemented by others such as the purin and mineral exchange. As the work was undertaken for the purpose of determining the nature rather than extent of the metabolic disturbances, and the labor involved in this investigation of nine cases is very considerable, a study of the calcium and magnesium metabolism was made only in one instance.

Fig. 14 (Case 9).—Extreme macroglossia in a boy aged 14. In this case there was an excessive hair growth over the entire body.

TABLE 1.—DIETARY DATA

Case Number	Nitrogen in Food	Calories in Food	Calories per Kilogram of Body Weight
1	9.03	1,275	55
2	9.38	1,765	30
3	11.11	1,895	31
4	9.38	1,765	38
5	11.11	1,895	56
6	9.03	1,275	48
7	9.03	1,275	53
8	9.03	1,275	39
9	9.03	1,275	31

TABLE 2.—PROTOCOLS OF URINARY ANALYSES

Case	Days	Volume, C.c.	Total Nitrogen, Gm.	Creatinin, Gm.	Creatin, Gm.	Creatin Plus Creatinin as Creatinin, Gm.
1	1	180	2.80	0.167	0.066	0.212
	2	340	3.94	0.151	0.176	0.303
	3	440	6.74	0.128	0.317	0.402*
	4	220	3.59	0.197	0.140	0.317†
2	1	720	5.21	0.279	0.210	0.461
	2	920	7.18	0.317	0.375	0.641†
	3	660	7.02	0.365	0.208	0.544*
3	1	440	6.84	0.209	0.622	0.745
	2	450	6.62	0.213	0.638	0.768
	3	540	7.20	0.211	0.604	0.732
4	1	540	7.53	0.254	0.669	0.832*
	2	450	5.61	0.198	0.528	0.662†
	3	440	5.25	0.209	0.592	0.719
5	1	450	8.47	0.128	0.621	0.663
	2	540	7.51	0.135	0.610	0.661
	3	720	7.96	0.136	0.598	0.651
6	1	1,040	6.18	0.104	0.578	0.602
	2	1,020	6.35	0.108	0.577	0.606
	3	680	6.42	0.080	0.530	0.546
7	1	660	4.99	0.102	0.404	0.460
	2	790	8.86	0.100	0.654	0.664
	3	690	7.91	0.122	0.518	0.569
8	1	420	7.11	0.086	0.230	0.284
	2	650	6.03	0.101	0.145	0.223
	3	590	3.95	0.079	0.140	0.200
9	1	850	8.35	0.160	0.617	0.691
	2	930	11.18	0.190	0.708	0.800
	3	610	7.88	0.146	0.583	0.649

* Slightly more than twenty-four hours.

† Slightly less than twenty-four hours. Sum of these two days, however, equals forty-eight hours.

TABLE 3.—URINARY CREATININ AND CREATIN PER KILOGRAM OF BODY WEIGHT *

Case	Creatinin, Mg.	Creatin, Mg.	Case	Creatinin, Mg.	Creatin, Mg.
1	6.8	7.5	6	4.2	23.0
2	5.2	4.3	7	4.0	19.5
3	3.4	10.0	8	2.8	5.4
4	4.7	12.8	9	4.1	15.9
5	3.9	17.9			

* Average of three twenty-four hour periods in all cases except Case 1, which is a four day average.

TABLE 4.—BLOOD ANALYSES. MILLIGRAMS PER 100 C.C.

Case	Creatinin	Creatin	Urea Nitrogen
1	0.52	6.8	18.7
2	0.45	5.8	
3	0.48	11.3	18.5
4	0.27	10.8	
5	0.55	6.9	
6	0.36	7.1	21.6
7	0.43	6.9	
8	0.48	6.6	8.9
9	0.28	7.2	22.4

ANALYTIC METHODS

Urine:

Creatinin according to Folin.[1]
Creatin according to Benedict.[2]
Glucose according to Pavy-Kumagawa.[3]
Calcium and magnesium according to McCrudden.[4]

Feces:

Calcium and magnesium according to McCrudden.[4]

Blood:

Urea nitrogen according to Van Slyke and Cullen.[5]
Creatinin according to Folin.[6]
Creatin according to Benedict and Myers.[7]
Blood sugar according to Epstein's modification of Lewis and Benedict's method.[8]

1. Folin, O.: Ztschr. f. physiol. Chem., 1904, **41,** 222.
2. Benedict, S. R.: Jour. Biol. Chem., 1914, **18,** 191.
3. Analyse des Harns, Neubauer-Huppert, 1910, **1,** 399.
4. McCrudden, F. H.: Jour. Biol. Chem., 1911, **10,** 187.
5. Van Slyke, D. D., and Cullen, G. E.: Jour. Biol. Chem., 1914, **19,** 211.
6. Folin, O.: Jour. Biol. Chem., 1916, **28,** 349.
7. Benedict, F. G., and Myers, V. C.: Am. Jour. Physiol., 1907, **18,** 397.
8. Epstein, A. A.: Jour. Am. Med. Assn., 1914, **63,** 1667.

EXPERIMENTAL RESULTS

The daily protocols of the urinary findings are grouped in Table 2. In contradistinction to the results of many metabolic studies on patients those obtained in this series of nine cases are definite and uniform throughout. They all show certain abnormalities in the creatinin-creatin and carbohydrate metabolism, as is emphasized in the following summary of our findings.

SUMMARY OF EXPERIMENTAL RESULTS

1. Marked decrease in the preformed creatinin in the urine.
2. Abnormal presence of creatin in the urine.
3. Low values of creatinin in the blood.
4. Normal amount of creatin in the blood.
5. Hypoglycemia.
6. Delayed glucose utilization (hourly blood sugar curve).

DETAILED RESULTS

Urinary Creatinin: The creatinin excretion showed its well known tendency to bear no definite relation to the total nitrogen excretion. Normally, about from 17 to 22 mg. of creatinin per kilogram body weight is excreted on a creatinin-creatin-free diet. As is evident from Table 3, only one-sixth to one-third of the usual amount was found in our series. Although reduced in all cases, the amount present seems to bear a certain relation to the severity of the clinical symptoms, for the creatinin was usually decreased more in the severer than in the lighter cases.

Urinary Creatin: Moderate amounts of this abnormal constituent of human urine were present in each case. The amount of creatin excreted in eight of the nine cases exceeded the creatinin.

Blood Creatinin: The values obtained by us vary from 0.27 mg. to 0.55 mg. of creatinin per 100 c.c. of blood. If the normal value is from 1 to 2 mg. per 100 c.c., as has been generally accepted, the blood creatinin of our muscular dystrophy cases is distinctly low. Unfortunately, the accuracy of blood creatinin determinations is still open to some criticism,[9] and may be found to be normally lower than is generally supposed. We therefore prefer at present not to draw definite conclusions from these observations. The apparently low values may, however, bear a relation to the low level of the urinary creatinin. The sum of creatinin plus creatin is generally below normal.

Blood Creatin: This was found to range nearly within normal limits in every case. It is to be remarked that the appearance of creatin

9. Gettler, A. O.: Jour. Biol. Chem., 1917, **29**, 47.

in the urine was unaccompanied by an increase in the creatin of the blood.

Blood Glucose: A definite hypoglycemia was demonstrated in our cases. The blood was examined in the morning before breakfast in order to avoid the influence of food. Repeated examinations showed the blood sugar to remain constantly at a low level. Although low blood sugar values are observed at times under those conditions in normal persons, such observations are infrequent and inconstant.

Carbohydrate utilization has been observed in our laboratory for some time. According to an unreported study the administration of 1.75 gm. of glucose per kilogram of body weight in 40 per cent. solution causes a characteristic rise in the blood sugar of normal individuals, the fasting blood sugar level being reattained one and one-half to two hours after ingestion. In possession of these data it was deemed advisable to make similar examinations in our dystrophy cases.

TABLE 5.—Blood and Urine Examination for Carbohydrate Assimilation

Case	Blood Glucose in per Cent.						Urinary Glucose Twenty-Four Hours, Gm.
	Fasting	After Glucose Ingestion					
		1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	
1	0.086	0.110	0.083	.....	.....	.....	Negative
2	0.065	0.146	0.156	0.117	0.078	.....	Trace
3	0.070	0.110	0.096	0.082	0.071	.....	2.5
4	0.080	0.198	0.196	0.0	0.127	0.062	3.7
5	0.067	0.113	0.069	.....	.....	.....	Trace
6	0.080	.....	0.115	0.096	0.083	.....	0.27
7	0.085	0.123	0.080	.....	.....	.....	Negative
8	0.073	0.131	0.192	0.077	.....	.....	Negative
9	0.066	0.127	0.095	0.090	0.063	.....	Negative

The results of these studies appear in Table 5. In each case the blood sugar was determined in the morning after a night's fast. This was followed by the ingestion of 1.75 gm. of glucose per kilogram in 40 per cent. solution. Blood sugar estimations were then made at hourly intervals. The results of these examinations bring out the fact that there is a distinct delay in the disappearance of carbohydrate from the blood of five out of nine cases, the normal blood sugar value not being reattained until the end of the fourth or fifth hour after glucose ingestion instead of previous to the end of the second hour, which is the rule in normal subjects.

It is interesting to observe that we are here probably dealing with a real defect in the proper removal of glucose from the blood, as will

now be explained. After ingestion of the measured amount of glucose the highest point of the resulting rise in the blood sugar represented a large percentile increase over the fasting blood sugar level. This increase amounted to about 65 per cent. on an average of the fasting value, whereas the normal rise is only about 20 per cent. under precisely the same conditions. As would be expected in view of the hypoglycemia, the absolute sugar values are not generally elevated more than in normal subjects undergoing the tolerance test.[10]

The significance of these findings will be discussed later. The definite presence of glycosuria following the sugar ingestion in five out of nine cases is another sign of the inability of these patients to assimilate carbohydrates in the usual manner, for normal persons rarely react with glycosuria after the ingestion of sugar in the amount given here

The total urinary nitrogen excretion was low in all cases. Complete nitrogen balances were not attempted, but judging from a comparison of the nitrogen of the food taken to that of the urine, there is an evident tendency to retention of nitrogen. This was unexpected, as the creatinin-creatin-free diet was low in nitrogen.

Blood urea nitrogen determinations were made as a check in five cases and found to present no striking deviations from the normal.

TABLE 6.—Calcium and Magnesium Exchange, Case 9

	Day	Intake, Gm.	Output		Balance, Gm.
			Urine, Gm.	Feces, Gm.	
Calcium oxid	1	1.83	0.14	0.35	1.34
	2	1.83	0.10	0.35	1.38
	3	1.83	0.12	0.35	1.36
Magnesium oxid	1	0.53	0.04	0.14	0.35
	2	0.53	0.06	0.14	0.33
	3	0.53	0.06	0.14	0.33

The calcium and magnesium exchange was studied over a short period in Case 9. The feces were demarcated with carmin at the beginning and end of the experimental period and the daily excretion averaged from the total obtained. The urine was analyzed daily. A large retention of both calcium and magnesium is evident from Table 6, in which the results are collected. On a diet containing an adequate

10. Case 4 showed glycosuria on a normal diet and is to be regarded as complicated with a tendency to diabetes. The blood sugar values are accordingly omitted in obtaining the average percentile increase in the tolerance test.

amount of calcium, it was found that the calcium and magnesium output in both urine and feces, as well as their total excretion, was quite small. A large retention of these mineral elements was evidently taking place here. Whether a low calcium and magnesium output is a constant feature in muscular dystrophy is a question open for future decision by means of extended metabolic studies.

DISCUSSION

Creatinin-Creatin Metabolism. — Though we are still far from adequately understanding the metabolism of these substances, a definite connection between them and the muscle metabolism is fairly well established. The well known occurrence of considerable amounts of creatin in muscle and other facts of more purely scientific interest support this view. This matter has also been the subject of considerable clinical study. In reviewing such results one must bear in mind that in some instances only the total creatinin, that is, creatinin plus creatin has been followed. Thus Pemberton[11] has reported a case of myasthenia gravis with a total creatinin output of 0.59 gm. daily, namely, a reduced excretion. Such examinations of the urine are not very instructive for they fail to differentiate between creatinin and creatin. This is important, as these substances have such strikingly different fates in the organism. Thus, Janney[12] administered a large dose of Kendall's thyroid hormone to a fasting dog. There resulted the clinical picture of hyperthyroidism accompanied by an enormous breakdown of body tissue and rise in total nitrogen and purin metabolism, also the appearance of creatin in considerable amounts in the urine. The creatinin, however, remained utterly unchanged in spite of the hyperpyrexia and other toxic symptoms present. We are thus forced to accept that different factors may control the metabolism of creatinin and creatin, as Folin first pointed out. Shaffer[13] in an important study which should be better known clinically, came to the conclusion that the urinary creatinin was a measure of the muscular efficiency of the patient. This view receives a certain substantiation in the fact that in various states of muscular weakness, the creatinin excretion is decidedly lowered. Such are exophthalmic goiter, myasthenia gravis, myotonia congenita and muscular dystrophy. For the last disease, Spriggs,[14] Levene and Kristeller[15] and the present writers

11. Pemberton, R.: Am. Jour. Med. Sc., 1910, **139,** 816.
12. Article in course of preparation.
13. Shaffer, P. A.: Am. Jour. Physiol., 1908, **23,** 1.
14. Spriggs, E. I.: Biochem. Jour., 1907, **2,** 206.
15. Levene, P. A., and Kristeller, L.: Am. Jour. Physiol., 1909, **24,** 45.

report low creatinin values. McCrudden and Sargent's[16] case is exceptional in this respect, since in that case normal values for creatinin were found.

The blood creatinin in muscular dystrophy has been previously little studied. McCrudden and Sargent report normal values in their single case. In view of the low urinary values found in our series of nine cases, one would expect low blood creatinin values, which we actually did find, but accept only with reservation as previously explained.

The appearance of creatin in human urine if the diet is creatin-free is pathologic. Creatin is excreted in conditions involving active-muscle breakdown. Thus, it has been observed in toxic and febrile states, in muscular diseases, and in inanition. During uterine involution the greatest amounts have been reported.[17] There seems little doubt of its constant presence when sought for in muscular dystrophy. Levene and Kristeller detected it in five cases, we in every case studied. Blood creatin in McCrudden and Sargent's case and our own cases presented no striking abnormalities. In our cases the total urinary creatinin plus creatin was reduced. Our normal values for creatin in the blood do not therefore exclude the possibility of a *relative* increase of blood creatin.

The carbohydrate metabolism in muscular dystrophy has been hitherto studied only in isolated instances. McCrudden and Sargent's observation of hypoglycemia in a single case has been later corroborated by them in other cases.[18] Our observations have been alluded to. That the metabolism of carbohydrate is actually delayed is shown by the tolerance tests.

Evidence Indicative of the Endocrine Nature of Muscular Dystrophy.—(*a*) *Pathologic and Clinical.*—In attempting to coordinate the complex manifestations of this interesting and relatively rare disease, the older point of view that it is limited to the muscle obviously must be abandoned. A purely nervous origin of muscular dystrophy can also be excluded, as lesions of the central or peripheral neurons are not recorded in the great majority of cases. In view of the articular, osseous and tendon changes reported by various observers, it is indeed evident that muscular dystrophy has a more general pathology.

We may now discuss the osseous changes. These were present in nearly all our series. It is very probable that if roentgenographic studies were regularly made in such cases, increased numbers would

16. McCrudden, F. H., and Sargent, C. S.: The Archives Int. Med., 1916, **17,** 465.

17. See Footnote 13.

18. Verbal communication to the authors.

show the bony changes to be rather constant. The osseous lesions have been usually ascribed to atrophy from disuse. It is very questionable, however, whether this is the true explanation. Thus Tixier and Roederer[19] report four cases of muscular dystrophy exhibiting, aside from myopathy, osseous changes resembling osteomalacia and dwarfism. Three of the cases having this significant syndrome were children of the same parents. This type of osteodystrophy was first described by Hutinel[20] in 1911. Hahn[21] likewise points out that the bone changes are not those of disuse.

Sterling[22] reports a significant and instructive case of simultaneous osseous changes and muscular dystrophy. The case is not definitely classifiable. The osseous changes in this instance are worthy of note and were specially studied. The muscle atrophy affected both upper and lower extremities, was primary, and appears to have been a dystrophy. The patient was a healthy boy of 17 with negative heredity. The malady developed gradually, beginning two years before admission with paresis and atrophy of the lower limbs. Pain in the knee joints appeared three months later, followed about a year later by objective osseous changes in the knee and ankle joints. A year subsequently the upper extremities became similarly affected, with elbow and wrist joints and deformity of the thorax and spinal column. Roentgen-ray examination showed decalcification of the epiphyses and to a lesser extent of the diaphyses. The osseous enlargements in this case were found to be due to separations which passed transversely through the bone, causing wide gaps in tissue, and in which a reconstructive callous formation of osteoid nature was found. Microscopically, the pathologic process suggested osteomalacia. Clinically, the bone changes are those seen in the course of exophthalmic goiter as described by von Jaksch and Rotky.[23]

Von Jaksch and Rotky's observation is pertinent and worthy of direct reference. The patient described by these authors was a young woman of 20 who had symptoms of exophthalmic goiter and in whom the superior and inferior thyroid arteries were ligated. After temporary recession of symptoms for two years, painful enlargements appeared at the distal portions of the bones of both forearms, with similar osseous changes in the bones of the legs and the pelvis. The thorax became deformed as a result of kyphoscoliosis. There was exquisite tenderness of the entire skeletal structure. Roentgenograms

19. Tixier, L., and Roederer, C.: Presse méd., 1913, **21,** 95.
20. Hutinel, V.: Gaz. d. hôp., 1912, **85,** 27.
21. Hahn, F.: Ztschr. f. Nervenh., 1901, **20,** 137.
22. Sterling, W.: Ztschr. f. d. ges. Neurol. u. Psychiat., 1913, **19,** 241.
23. Von Jaksch, R., and Rotky, H.: Festschr. a. d. Geb. d. Roentgenstrahlen, 1908-1909, **13,** 1.

revealed separations on cross section of the bones, with formation of open clefts with callous formations of osteoid nature. The portions of the bones thus affected became atrophic. The authors reject assumption of an incidental bone disease but regard the osseous changes as associated with the dysthyroidism or hypothyroidism. The condition is regarded by Sterling as pointing to a faulty metabolism on the basis of hypothyroidism.

The case reported by Boggs[24] shows the relationship between primary muscle degeneration and pathologic changes in bone and nerve tissue. Other than the record of thyroid atrophy, the observer gives no suggestion as to the endocrinic symptoms. The patient, 23 years old, suffered with multiple congenital osteochondromas. His father was similarly affected. Primary optic atrophy and nuclear acoustic nerve changes were found.

Other changes indicative of general endocrine disturbance are numerous. They include dryness and abnormal pigmentation of the skin, brittleness of the hair, hypertrichosis, trophic changes in the nails, unusual distribution of the subcutaneous fat and both hypertrophy and underdevelopment of the genitalia. All of these changes were observed in our representative series of cases as the abstracts from the case histories and photographs record.

Also characteristic of several of our cases was retardation of growth, a symptom definitely indicating endocrine hypofunction. Collins and Climenko[25] have reported growth anomalies in various cases. Retardation of growth in muscular dystrophy has also been reported by Tixier and Roederer. It is of course conceivable that the inactivity of consequent lowered nutrition of muscular dystrophic subjects might of themselves cause failure of full development, but the peculiar osseous changes in these cases show, as we have observed, that a true defect of metabolism is present.

(*b*) *Evidence from Metabolic Studies.*—Do the metabolic studies carried out by previous workers and by ourselves lend support to the endocrine origin of muscular dystrophy? The relationship of decreased creatinin excretion to a possible endocrine origin is not obvious, for in a very wide variety of morbid conditions the creatinin output is low. If we accept Shaffer's hypothesis, the decreased creatinin output would merely be due to the decreased muscular activity. This, however, is likely. Another reason for decreased creatinin excretion, however, may lie in the abnormal presence of creatin in the urine, for it is known

24. Boggs, Th. R.: Bull. Johns Hopkins Hospital, 1913, **24**, 210.

25. Collins and Climenko: Post Graduate, Twenty-Fifth Anniversary Number, 1908.

that the creatin so appearing is apparently excreted at the expense of the creatinin which is consequently eliminated in diminished amounts.

Evidently we must seek further for more tangible metabolic evidence. This is afforded by a consideration of the laws governing creatin metabolism. We have seen that the appearance of creatin in the urine is a sign of destruction of muscle tissue. Mendel and Rose[26] demonstrated that the creatin content of muscle is increased in starvation. Creatin excretion in the absence of a toxic or febrile cause represents a sign of undernutrition of muscle, a fact of considerable importance in the present consideration. The controlling factors of creatin formation were studied by Mendel and Rose[27] in another important research. These investigators found that the creatin immediately disappeared from the urine when carbohydrates were ingested by the experimental subjects. That carbohydrates alone exerted this influence was shown in other experiments demonstrating that protein or fat ingestion failed to cause creatinuria to cease. An insufficient supply of carbohydrate to the muscles is then to be regarded as a prime factor in producing excretion of creatin.

These considerations led us to investigate carefully the carbohydrate metabolism of muscular dystrophy. The constant presence of hypoglycemia and evidence of delayed glucose utilization were found, as has been reported in previous pages. These results permit an insight into the pathogenesis of the myopathy under discussion, for they make it probable that these defects in the carbohydrate metabolism are intimately connected with, if not directly causative of, the metabolic picture of the disease. It seems likely that the muscles in this condition undergo weakness, atrophy and degeneration as the supply of their normal carbohydrate pabulum is interfered with. As a result, creatin appears in the urine, and the creatinin excretion is accordingly lowered. It is a striking fact that the creatinin-creatin metabolism of muscular dystrophy closely resembles that of fasting. In these cases also a tendency has been reported for the creatinin to decrease and for the creatin to appear in the urine. It would seem that the muscles of the subject affected with this myopathy are likewise suffering from lack of nutriment and therefore undergo retrogressive changes similar to those seen in starvation. Even in prolonged fasting the blood sugar is maintained at the usual level, showing the vital importance of this nutritive material. Hypoglycemia could be expected to lead, therefore, to a great loss of muscle substance. This is exemplified by phlorizin diabetes, which is characterized by hypoglycemia and rapid emaciation.

26. Mendel, L. B., and Rose, W. C.: Jour. Biol. Chem., 1910-1911, **10,** 255.
27. Mendel, L. B., and Rose, W. C.: Jour. Biol. Chem., 1910-1911, **10,** 213.

Other factors may, however, play a rôle in the production of these phlorizin poisoning symptoms.

Our contention that the ultimate origin of muscular dystrophy lies in an endocrine dystrophy is further strongly supported by clinical and experimental analogies, which will now be detailed. Practically all the clinical symptoms and metabolic signs already referred to have been observed in well known hypofunctional conditions of the ductless glands.

Hypoglycemia in Other Endocrine Conditions. — In myxedema, Geyelin[28] has reported hypoglycemia. In cretinism we have observed hypoglycemia accompanied by creatin in the urine. A delay in carbohydrate utilization in a creatin and several exophthalmic goiter patients studied by us was demonstrated by blood sugar curves.[29] Cushing[30] called attention to hypoglycemia in dyspituitarism. It has also been observed in Addison's disease.[31] Muscular asthenia is not necessarily accompanied by a low blood sugar value. Thus, in diabetes and some cases of exophthalmic goiter, hyperglycemia and muscular weakness coexist. The causes of the hyperglycemia in these diseases are, however, different. In diabetes it is probably due to inability to oxidize and synthetically utilize carbohydrate, while in exophthalmic goiter the increased blood sugar may be the result of toxic breakdown of protein characteristic of this disease.

Hypoglycemia Not Due to Disuse.—If hypoglycemia is a characteristic of deficient endocrine function and is not the result of a lessened requirement for carbohydrate due to smaller quantities of muscle tissue to be nourished, one should not expect to observe it in chronic arthritis cases. McCrudden and Sargent, who very properly raise this point, accordingly made blood sugar determinations in several of such cases and found normal values. We have extended these control studies to five similar cases with secondary generalized muscle atrophy and have likewise found the blood glucose at or slightly above its normal level. The values obtained by us were as follows:

Case, W. M., arthritis deformans, 0.102 per cent., 0.104 per cent. Case, M. R., chronic polyarthritis, 0.122 per cent., 0.124 per cent. Case, M. S., arthritis deformans, 0.107 per cent. Case, M. L., chronic infectious polyarthritis, 0.104 per cent., 0.100 per cent. Case, M. C., chronic polyarthritis, 0.103 per cent., 0.109 per cent.

28. Geyelin, H. R.: The Archives Int. Med., 1915, **16,** 975.

29. Unpublished experiments.

30. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia: J. B. Lippincott Company, 1910, p. 130.

31. Porges, O.: Ztschr. f. klin. Med., 1909-1910, **69,** 341; Janney: Unreported observation.

Experimental Demonstration of Hypoglycemia After Removal of Ductless Glands.—If the metabolic picture which we found in muscular dystrophy is really the result of dysfunction of the endocrine organs, it should be possible to reproduce it essentially through removal of one or more ductless glands in animal experiments. In the case of the epinephric bodies some data is available, as hypoglycemia has been reported after epinephrectomy.[32] These experiments are subject, however, to some question, as death ensues under these circumstances, and the decrease in the blood sugar has been explained as an immediate antemortem phenomenon.[33]

Recent experiments by Janney and Isaacson[34] are not open to this objection and seem conclusive as far as the thyroid may be concerned. The blood glucose, blood and urinary sugar tolerance, also creatinin creatin metabolism were studied in a series of dogs before and after thyroidectomy. As a result, a marked hypoglycemia, delayed blood sugar curve and other metabolic changes were observed. These experiments will be reported in detail and will not therefore be reviewed here. Suffice it to say that the changes described were quite definite and seem to represent the first clear cut demonstration that the abolition of the function of an endocrine organ leads to hypoglycemia. Indeed, the knowledge gained by this work has been applied in the present clinical study.

CHEMOPATHOLOGIC CONSIDERATIONS

The so-called pseudohypertrophy of certain muscle groups is characteristic of this disease. Fulda's[35] view that the muscle enlargements are physiologic hypertrophy is not justified by the limited material presented by him. A real hypertrophy is an increase in the number of normal muscle fibers and the bulk of sarcoplasm present in the muscle. The findings in muscular dystrophy are not these. Thus Morpurgo[36] observed that normal hypertrophied muscle did not show the splitting and loss of angular contour of the fibers, proliferation of connective tissue and fat deposition exhibited by specimens from muscular dystrophy cases. Spiller[37] in his pathologic studies thought that the many nuclei present in dystrophic muscle possibly indicative of growth. He, however, very properly emphasized that the other histologic anomalies were the same changes originally described by Erb, hence degenerative

32. Bierry, H., and Malloizel, L.: Compt. rend. Soc. de biol., 1908, **65,** 232.
33. Frank, E., and Isaac, S.: Ztschr. f. exper. Path. u. Therap., 1909, **7,** 326.
34. Janney, N. W., and Isaacson, V. I.: Proc Soc. Exper. Biol. and Med., 1917, **14,** 99.
35. Fulda, F.: Deutsch. Arch. f. klin. Med., 1894-1895, **54,** 525.
36. Morpurgo, B.: Virchows Arch. f. path. Anat., 1897, **150,** 522.
37. Spiller, W. G.: Med. Rec., New York, 1898, **54,** 9.

in character. Darkschewitsch[38] says that in the various types of muscular atrophies it is not uncommon to find besides the atrophic fibers, others of a size far in excess of normal muscle. Hence the nuclear proliferation observed by Spiller in muscular dystrophy may, in our opinion, represent an imperfect effort toward compensation for the great number of fibers already atrophied.

The experimental data presented in this article and the foregoing discussion emphasize the important part played by the disturbance of carbohydrate metabolism in the pathology of muscular dystrophy. There remains to consider whether this new data will aid us in interpreting the histologic phenomena peculiar to the disease. It is known how important carbohydrate pabulum is to muscle work and repair. The blood of muscular dystrophy patients, as we have seen, supplies a greatly diminished amount of carbohydrate to the muscles. The effect can readily be supposed to be a tendency to extensive degeneration of muscular tissue. This might account for the histologic picture. The lipomatosis of the dystrophic muscle groups is not a result of normal catabolism, but is a metabolic phenomenon distinctive of this muscle disease. The defective carbohydrate metabolism may very possibly have a causal connection with these fat deposits, for it is known that other organs such as the liver are apt to become the special seat of fatty depositions when their carbohydrate metabolism becomes abnormal. It is a striking fact that the dystrophic pseudohypertrophy is usually limited to certain muscle groups, calves, thighs and deltoids, which are used very constantly. In explanation, it may be suggested that the profoundest metabolic disturbances may take place in such muscle groups because their constant activity may render the repair processes, already inhibited on account of hypoglycemia, inadequate. As a result the degenerative changes already described may occur. This hypothesis seems attractive.

In our series several cases showed unusual depositions of fat in the mammary and inguinal regions. The case of Levi and de Rothschild,[39] quoted by Délille,[40] exhibited at the seventh year an asthenic myopathy associated with lipomatosis and other symptoms indicative of endocrine disease. Such abnormalities in the distribution of fat are present in other diseases as hypopituitarism, likewise characterized by disturbances in the carbohydrate metabolism. Thus it will be remembered that 50 per cent. of diabetics give a history of previous adiposity.

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38. Handbuch der Pathologischen Anatomie des Nervensystems, Berlin, 1904, **1,** 1259, chapter on "Hypertrophie der Muskeln."

39. Levi, L., and de Rothschild, H.: Rev. d'hyg. et de méd. inf., 1907, **6,** 309.

40. Délille, A.: L'hypophyse et la Médication Hypophysaire, Paris, 1909.

QUESTION AS TO WHAT ENDOCRINE GLANDS ARE INVOLVED IN MUSCULAR DYSTROPHY

Opinions as to the nature of the endocrine disfunction are divergent. Indeed, even the pertinent inquiry has been raised by Parhon and Savini[41] as to whether the various atrophic ductless glands observed in dystrophy cases are primary or secondary. Following this line of reasoning these authors devised an ingenious hypothesis that the myopathic changes of the disease under discussion might be favorably influenced by building material already present in the muscle. Two children were accordingly fed with an extract of fetal muscle. Improvement is said to have followed this treatment.

Most authors, however, incline to consider a primary endocrine disturbance. Various attempts have been made to elucidate its exact nature. Thus, Markeloff[42] at Petrograd injected various glandular substances into dogs and measured the muscular activity with the ergograph or kymograph on electric stimulation. The thyroid, hypophysis, suprarenals and testicles were found to stimulate muscular functional activity, the remaining endocrine glands being inhibitory. As regards the special gland involved, there is little accord. Pende[43] holds that the thymus is involved, suggesting thymic asthma as a cause of the dyspneic attacks in muscular dystrophy, calling attention to the splenic hyperplasia and transformation of the bone marrow. Such dyspneic attacks may well be due, however, to the exhaustion of the respiratory muscular mechanism.

The theory of Chvostek[44] and of Lundborg[45] that the hypersecretion and hyposecretion of the parathyroids stands in causative relation to myasthenia gravis and tetany, respectively, finds strong opponents in Haberfeld[46] and other observers. The effect of opotherapy in the asthenias has been discussed by Carnot.[47] Claude[48] describes an instructive case of myopathy associated with anomalies described by this author as pluriglandular insufficiency and tentatively seeks the cause of muscular dystrophy in abnormal activity of the hypophysis and pineal glands. Gautier[49] in making observations on thyroid therapy quotes

41. Parhon, C. J., and Savini, E.: Rev. Neurol., 1914-1915, **22,** 1215.
42. Markeloff, G. J.: Russk. Vrach, 1913, **12,** 1291. For German version see Zentralbl. f. d. ges. Chir. u. i. Grenzgeb., 1913-1914, **3,** 545.
43. Pende, N.: Endocrinologia, Milan, 1916, p. 996.
44. Chvostek, F.: Wien. klin. Wchnschr., 1908, **21,** 37.
45. Lundborg, H.: Deutsch. Ztschr. f. Nervenh., 1904, **27,** 217.
46. Haberfeld, W.: Virchows Arch. f. Path. Anat., 1911, **203,** 282.
47. Carnot, P.: Opotherapie, Monograph, Paris, 1911.
48. Claude, H.: Rev. neurol., 1911, **21,** 257.
49. Gautier, G.: L'opotherapie thyroidemie, monograph, Paris, 1913.

Lepine's[50] and Egger's[51] favorable results in cases of primary myopathy. Levi and de Rothschild, again, publish their favorable results on primary myopathies with hypophysis gland preparations. McCrudden and Sargent's patient improved on epinephrin and pituitrin.

In our own series roentgenographic studies were made with a view of determining a possible pineal involvement. In two cases only were distinct shadows found in locations ascribed to the pineal. That these shadows represent actual pathologic conditions in the pineal body is open to serious question. Timme[52] in an interesting paper reports a probable pineal involvement in four cases from the same family. This author calls attention to the muscular weakness observed in pineal disease and emphasizes the possible pineal origin of certain cases of muscular dystrophy.

The thyroid gland seems in some instances to bear a relation to muscular dystrophy. The similarity of the osseous changes in muscular dystrophy and thyroid disease has been alluded to previously. Boveri[53] has reported several muscular dystrophy cases in which exophthalmic goiter was also present. Von Werdt's[54] case of muscular dystrophy was found to have at postmortem a colloid struma of the thyroid and changes in other ductless glands. Prager's[55] case was evidently one of muscular dystrophy in a hyperthyroid subject.

In our own series the one positive clue as to the involvement of a special endocrine gland was presented by Case 9. In this case there was a definite combination of acromegaly with the typical pseudohypertrophic lesions of muscular dystrophy. This case is strong evidence in favor of a causative connection between dyspituitarism and muscular dystrophy. Bregman[56] also mentions among his several cases a boy of 19 years affected with the so-called heredity type of dystrophy whose hands and feet presented a disproportionate development of the bony framework which did not fit in with the otherwise very delicate configuration of the body. Similar observations were made by Eulenberg[57] and were referred by him to atrophic changes in the bone system in analogy with the muscular changes.

Awkward as this is from the standpoint of therapy, we must face the possibility of muscular dystrophy and perhaps other so-called primary myopathies being in reality merely symptom complexes caused

50. Lepine, R.: Lyon méd., 1896, **82,** 35.
51. Egger, F.: Arch. f. Psychiat., 1896-1897, **29,** 400.
52. Timme, W.: The Archives Int. Med., 1917, **19,** 79.
53. Boveri, P.: Semaine méd., 1910, **30,** 145.
54. Von Werdt, F.: Frankfort Ztschr. f. Pathol., 1908-1909, **2,** 577.
55. Prager, M.: Dissertation (Erlangen) Fürth, A. Schroeder, 1891.
56. Bregman, L. E.: Deutsch. Ztschr. f. Nervenh., 1898-1899, **14,** 254.
57. Eulenburg, A.: Deutsch. Med. Wchnschr., 1896, **22,** 458.

by deficient function, not of one but of various endocrine organs separately or coincidently affected. This view seems reasonable when one considers that the symptoms which are known to represent dysfunction of one endocrine gland are often very similar or identical with the manifestations of the affection of another ductless gland. Thus, stoppage of growth, adiposity and defective bone formation are known to result from lesions of either pituitary, thyroid or sex glands. If then, these symptoms are connected with such widely different organs, it seems not improbable that muscular dystrophy may likewise prove to represent a symptom complex capable of being caused by dysfunction of various ductless glands singly or together. Therefore, we do not ascribe musclar dystrophy to hypothyroidism, as might seem justified from our experiments already alluded to. The fact that the hypophysis was unquestionably affected in one case and the pineal possibly in two others, illustrates how difficult it would be to explain our series of cases on a hypothyroid or hypophysis basis. Finally, it is hoped that the present research may, in helping to establish the endocrine origin of muscular dystrophy, serve to stimulate therapeutic efforts as well as metabolic investigations of the so-called primary myopathies.

STUDIES IN ACUTE NEPHRITIS*

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In this communication I wish to present certain observations recently made on three cases of acute nephritis that were admitted to the medical wards of the Royal Victoria Hospital. The patients were admitted at the onset of the condition and were studied until convalescence was well established. Two of the cases have been subsequently followed for a prolonged period. Observations were made as nearly simultaneously as possible by four methods which I believe give the most valuable data obtainable in kidney function studies. These four methods are (1) the test meal; (2) the estimation of the rate of excretion of urea; (3) the determination of the calculated and actual blood plasma chlorids in coordination with their rate of excretion, and (4) the phenolsulphonephthalein test.

The Nephritic Test Meal. — The nephritic, or better the kidney function, test meal, as first advanced by Hedinger and Schlayer,[1] and later elaborated by Mosenthal[2] and O'Hare,[3] has proved to be of great value in estimating the ability of the kidney to eliminate fluid, salt and nitrogen. After a study of some 200 meals, given in this clinic according to the Mosenthal technic, I think that the total balances of fluid, salt and nitrogen are of little value, as in most cases the intake is accurately known only during the twenty-four hours of the test. The three points which I consider to be of the most importance are (*a*) the volume of the night urine; (*b*) the variation of specific gravity throughout the twenty-four hours, and (*c*) the concentration of nitrogen at night. Even the last point, the ability of the kidneys to concentrate nitrogen at night, must be considered conservatively, since Mosenthal[4] recently has shown that there are certain kidneys, apparently normal in all other respects, that fail in this function.

Excretion of Urea and of Chlorids.—The rates of excretion of urea and of chlorids have been studied according to McLean's[5] method. For the former, we have derived both his index and the Ambard con-

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* From the medical Clinic of the Royal Victoria Hospital.
* I should like to express my appreciation of a grant from the James Cooper Fund of McGill University which made this work possible.

1. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med., 1914, **114,** 120.
2. Mosenthal: THE ARCHIVES INT. MED., 1915, **16,** 733.
3. O'Hare: THE ARCHIVES INT. MED., 1916, **17,** 711.
4. Personal Communication.
5. McLean: Jour. Exper. Med., 1915, **22,** 212.

stant; for the latter, the calculated and actual blood plasma chlorids, as well as the chlorid threshold.

The Phenolsulphonephthalein Test.—The phenolsulphonephthalein test has been performed according to Rowntree and Geraghty's[6] original technic, 0.006 gm. of the dye being injected intramuscularly into the lumbar region and ten minutes allowed for the dye to reach the kidneys. One and two hour specimens were collected.

The methods used are for

Total Nitrogen: Kjeldahl-Gunning modification.

Urea: Van Slyke and Cullen's[7] modification of Marshall's urease method.

Ammonia: Folin's[8] micromethod.

Chlorids (in both blood plasma and urine): McLean and Van Slyke's[9] method.

Blood Sugar: Lewis and Benedict's[10] original technic.

REPORT OF CASES

A brief synopsis of the three cases follows, and the laboratory notes are given in full.

CASE 1. (Medical No. 24738). *History.*—A man, aged 55, was admitted to the Royal Victoria Hospital, Oct. 24, 1916, complaining of swelling of feet and legs, shortness of breath, and headache.

The patient was in usual health until four days previously, when he noticed swelling and soreness of the left ankle. The next day his right ankle also became sore and swollen, which was followed by a generalized edema of both legs. At this time he began to suffer from headaches and shortness of breath on exertion. Two days later the headaches became much worse. His personal history was negative except that he had scarlet fever when a child, and there was nothing of importance in his family history.

Examination.—He was a well developed, middle aged man, the muscles were of good tone, but he was unable to lie on the left side without coughing and becoming dyspneic. The digestive, genito-urinary, locomotor and integumentary, lymphatic and nervous systems were normal; also the fundi were normal.

Respiratory System: At the right base behind there was a triangular area of dulness extending upward to the level of the seventh dorsal spine and laterally to the anterior axillary line. Over this area the percussion note was flat, tactile fremitus was absent, and breath and voice sounds were much diminished.

Cardi of Circulatory System: The pulse was regular but tension was increased. The cardiac transverse dulness was 14 cm. at the level of the fourth space; otherwise negative.

Temperature and Pulse: On admission there was a slight evening temperature of 100 F., which dropped very gradually, reaching the normal on November 27. While the evening temperature was present the pulse rate averaged from 90 to 100, dropping to a level of from 70 to 80 as the temperature fell.

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6. Rowntree and Geraghty: THE ARCHIVES INT. MED., 1912, **9**, 284.
7. Van Slyke and Cullen: Jour. Biol. Chem., 1914, **19**, 211.
8. Folin and MacCallum: Jour. Biol. Chem., 1912, **11**, 523.
9. McLean and Van Slyke: Jour. Biol. Chem., 1915, **21**, 361.
10. Lewis and Benedict: Jour. Biol. Chem., 1915, **22**, 61.

TABLE 1.—A Record of the Observations Made on the Rate of—

Case 1. Medical No. 24738—

Date	Weight, Kg.	Urine, per 24 Hours, C.c.	Urea				
			Gm. per Liter of Blood, Ur	Gm. per Liter of Urine, C	Gm. per 24 Hours D	McLean's Index	Ambard Constant
10/28/16	....	.....	.....	.....	.....	....	.....
11/ 6/16	69.8	2,160	0.858	14.16	30.57	17.0	0.194
11/14/16	66.4	3,456	0.870	10.00	34.56	19.6	0.181
11/20/16	65.9	3,000	0.852	7.16	21.48	10.8	0.243
12/ 1/16	63.2	3,888	0.780	2.97	11.55	4.6	0.371
12/ 8/16	62.0	4,992	0.810	2.07	10.33	3.2	0.442
12/14/16	61.1	3,744	0.810	2.97	11.11	4.3	0.391
12/23/16	60.3	2,880	1.530	9.19	28.51	5.2	0.329
1/ 2/17	60.9	3,768	1.140	4.96	18.43	4.8	0.370
1/10/17	59.5	4,176	0.600	2.94	12.26	8.9	0.269
1/13/17	60.4	5,112	0.570	1.65	8.43	4.6	0.370
1/25/17	60.2	4,872	0.420	2.37	11.54	15.0	0.212
2/ 2/17	63.9	3,792	0.390	5.37	20.35	43.5	0.110
2/ 9/17	63.9	4,104	0.570	4.74	19.45	18.4	0.188
2/16/17	64.1	3,792	0.480	4.06	15.46	19.0	0.185
2/23/17	65.7	5,472	0.540	4.65	25.44	25.7	0.159
3/ 9/17	66.4	5,592	0.660	4.65	25.99	17.4	0.192
3/24/17	66.7	1,800	0.630	14.34	25.81	33.1	0.139
4/ 6/17	76.5	2,568	0.510	10.06	25.82	42.0	0.124
4/20/17	68.3	4,320	0.585	6.66	28.77	28.5	0.149
5/ 4/17	68.4	3,696	0.510	7.74	28.56	40.0	0.126
5/18/17	68.5	5,328	0.630	4.11	21.89	14.7	0.210
6/ 1/17	69.2	2,040	0.585	14.04	28.64	40.5	0.126
6/22/17	67.5	5,000	0.585	5.29	26.45	23.5	0.165
7/ 6/17	68.1	3,552	0.540	3.99	14.16	12.7	0.226

—Urea and Chlorid Excretion and on Phenolsulphonephthalein Test
—Diagnosis: Acute Nephritis

Sodium Chlorid					Threshold	Phenolsulphonephthalein, Two Hours, per Cent.	Remarks
Gm. per Liter of Urine, C	Gm. per 24 Hours, D	Gm. per Liter of Plasma					
		Calculated	Actual	Difference			
....	.....	.....	.....	.....	.....	86	Edema of lower limbs
2.61	5.64	5.695	6.556	+0.861	6.381	..	Albumin = 8 gm. per liter
3.15	10.87	5.964	6.687	+0.723	6.343		
3.1	7.65	5.840	6.125	+0.285	5.905		
1.68	6.52	5.798	5.937	+0.139	5.759	Trace	Albumin, 2 gm. per liter
2.42	12.13	5.888	5.927	+0.039	5.669	Trace	
1.4	5.23	5.775	5.687	−0.088	5.532	15	
2.6	7.48	5.837	6.25	+0.413	6.023	20	
2.4	9.04	5.852	6.50	+0.647	6.267	..	No red blood cells
1.0	4.17	5.748	5.47	−0.278	5.342	24	Jan. 9, 1917, theophyllin, 15 grains
0.62	3.16	5.718	6.062	+0.344	5.964	..	Albumin, a trace
1.62	7.87	5.819	6.062	+0.243	5.863	41	Discharged Jan. 27, 1917
6.94	20.80	6.126	7.062	+0.936	6.556	42	Ate extra salt
6.0	24.62	6.092	7.062	+0.97	6.59	40	
3.25	12.31	5.906	6.750	+0.844	6.464	..	Albumin = 0
3.37	18.43	5.969	6.625	+0.656	6.276	40	
3.4	19.01	5.973	6.437	+0.464	6.084	46	
3.7	15.06	6.024	6.625	+0.601	6.221	41	
6.2	15.92	5.992	6.625	+0.633	6.253	34	
5.6	24.19	6.065	6.312	+0.247	5.867	51	Albumin = 0
5.7	21.06	6.037	6.312	+0.275	5.895	41	
2.4	12.78	5.881	6.000	+0.119	5.739	..	Albumin, a trace
7.7	15.70	6.006	6.062	+0.056	5.676	51	
2.6	13.0	5.89	5.937	+0.047	5.667	57	Albumin = 0
1.6	5.08	5.778	5.625	−0.153	5.467	56	

Blood Pressure: Oct. 24, 1916, the systolic pressure was 150, and the diastolic 115 mm. of mercury. These gradually dropped, the most prompt reduction taking place in the diastolic pressure.

BLOOD PRESSURE

Date	Systolic	Diastolic
Nov. 20, 1916	140	100
Jan. 4, 1917	140	90
Jan. 10, 1917	135	90
Jan. 15, 1917	130	95
Jan. 25, 1917	130	90
Feb. 3, 1917	150	110
March 9, 1917	144	92
April 20, 1917	140	90
May 4, 1917	124	90
June 1, 1917	126	80

Blood: Oct 26, 1916, the red blood cell count was 4,200,000; white blood cell count, 9,400, and the hemoglobin 50 per cent. (Sahli).

Urine: Oct 24, 1916. The urine was of an amber color with a "smoky" appearance, acid in reaction, with a specific gravity of 1,021. There were 8 gm. per liter of serum albumin and the microscopic examination showed large numbers of red blood cells, granular and cellular casts.

Oct. 28, 1916, 1,650 c.c. of opalescent, yellowish fluid were withdrawn from the right pleural cavity. The specific gravity was 1.012 and it contained 200 cells per cubic millimeter, mostly small mononuclears.

The results of the study of the kidney function are shown in the accompanying tables. Table 1 gives the observations made on the rate of urea and chlorid excretion as well as on the phenolsulphonephthalein test. The diet throughout the period of these observations is shown in Table 2, the dates indicating a change.

TABLE 2.—THE DIET GIVEN THROUGHOUT THE PERIOD OF OBSERVATIONS RECORDED IN TABLE 1.

Date	Diet	Sodium Chlorid	Fluid Total, C.c.
10/31/16	Restricted protein	.....	1,000
11/11/16	Low protein diet	Salt-free	1,000
12/ 8/16	Low protein diet	Salt-free	2,000
12/12/16	Protein, 52; fat, 60; carbohydrate, 100	Salt-free	2,000
12/17/16	Protein, 60; fat, 65; carbohydrate, 150	Salt-free	2,000
12/29/17	Low protein diet	Salt-free	2,000
1/26/17	Protein, 52; fat, 60; carbohydrate, 100	Salt-free	2,000
1/27/17 discharged	Restricted protein	Restricted salt in cooking; no free salt	

Three nephritic test meals that show the changes in function in relation to the rate of excretion of urea and chlorids are given in full. The first was administered during the period of acute inflammation, the second during that of greatly impaired function, and the third at the time of convalescence.

TABLE 3.—Results Observed After the Administration of Nephritic Test Meals.

Case 1: Nov. 15, 1916. Meal given during the period of acute inflammation

Time of Day	Urine, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8–10	122	1.015				
10–12	170	1.014				
12– 2	165	1.015				
2– 4	160	1.014				
4– 6	170	1.015				
6– 8	140	1.015				
Total day	927	.....	0.290	2.67	0.574	5.30
Night, 8–8	960	1.013	0.418	4.03	0.539	5.18
Total 24 hours	1,887	.....	.....	6.70	.....	10.48
Intake	1,760	.....	.....	8.4	.....	13.4
Balance	−127	.....	.....	+1.7	.....	+2.92

Case 1: Jan. 20, 1917. Meal given during period of greatly impaired function

8–10	168	1.013				
10–12	118	1.016				
12– 2	33	1.019				
2– 4	79	1.020				
4– 6	121	1.016				
6– 8	106	1.018				
Total day	625	.....	0.318	1.97	0.371	2.30
Night, 8–8	620	1.016	0.328	1.93	0.387	2.39
Total 24 hours	1,245	.....	.....	3.90	.....	4.69
Intake	1,760	.....	.....	8.5	.....	13.4
Balance	+515	.....	.....	+4.6	.....	+8.71

Case 1: March 23, 1917. Meal given during convalescence

8–10	108	1.022				
10–12	62	1.024				
12– 2	98	1.025				
2– 4	104	1.026				
4– 6	118	1.025				
6– 8	130	1.023				
Total day	615	.....	0.77	4.69	0.97	5.91
Night, 8–8	517	1.024	0.66	3.36	1.02	5.20
Total 24 hours	1,132	.....	.....	8.05	.....	11.11
Intake	1,700	.....	.....	8.5	.....	13.4
Balance	+628	.....	.....	+0.45	.....	+2.29

CASE 2 (Medical No. 25374). *History.*—A man, aged 30, was admitted to the Royal Victoria Hospital, March 6, 1917, complaining of "Cold in the chest." His present illness began ten days previously with a cold that was rapidly followed by a severe sore throat, hoarseness, and cough with expectoration. With the onset of cough he had several slight chills followed by sweats. For the previous week the urine had been of a dark brown color. His personal and family history were unimportant.

TABLE 4.—RESULTS OF THE STUDIES MADE ON THE RATE OF UREA AND—

Case 2. Medical No. 25374—

Date	Weight, Kg.	Urine, per 24 Hours, C.c.	Urea				
			Gm. per Liter of Blood, Ur	Gm. per Liter of Urine, C	Gm. per 24 Hours D	McLean's Index	Ambard Constant
3/ 9/17	76.0	1,104	0.540	10.78	11.88	15.8	0.208
3/15/17	75.4	1,584	0.570	17.38	27.52	42.0	0.124
3/28/17	71.4	936	0.555	23.4	21.84	43.0	0.122
4/ 4/17	71.7	1,056	0.360	18.79	19.82	83.0	0.068
4/10/17	70.4	1,632	0.435	17.44	28.44	80.0	0.089
4/17/17	71.7	1,920	0.345	12.28	23.57	87.0	0.086
4/24/17	71.7	4,368	0.252	7.68	32.58	94.0	0.083
5/ 1/17	71.8	2,712	0.285	10.0	27.12	133.0	0.069
5/ 8/17	72.3	864	0.270	16.2	13.90	95.0	0.082
5/16/17	72.6	1,464	0.255	13.68	19.15	135.0	0.069

Examination: He was a well developed and nourished young man. The physical examination was negative except for an inflamed throat and diffuse, large, moist râles over both sides of the chest. The fundi were normal.

On admission the temperature was 101 F., but it rapidly dropped to an evening temperature of 99 F., which was maintained until March 23.

Blood Pressure: Systolic, 130; diastolic, 70. Further estimations failed to show any variations.

Urine: March 7, 1917, this was observed to be brown and "smoky" with a specific gravity of 1.015; there were 4 gm. of albumin per liter, with red blood cells, cellular and granular casts.

Table 4 gives the results on the rate of urea and chlorid secretion and the phenolsulphonephthalein test.

CASE 3 (Medical No. 24890). *History.*—A boy, aged 15, was admitted to the Royal Victoria Hospital Dec. 3, 1916. The patient complained of swelling of face and ankles and difficulty in passing urine. He was in usual health until twelve days previously, when he caught cold. At the onset he had chilly sensations and his face and ankles became swollen. He had no polyuria, but during the previous week micturition had been painful. The patient had scarlet fever, with a normal convalescence, when 5 years of age. The family history was unimportant.

Examination: The patient was a fairly well nourished boy; the mucous membranes were pale and around both eyes and ankles there was marked edema. The examination was otherwise negative. The temperature was normal, also the fundi.

Blood Pressure

Date	Systolic	Diastolic
Dec. 4, 1916	130	80
March 2, 1917	140	88
April 20, 1917	120	60
May 4, 1917	128	88

—of Chlorid Excretion and the Phenolsulphonephthalein Test-

—Diagnosis: Acute Nephritis

Sodium Chlorid					Threshold	Phenolsulphonephthalein, Two Hours, per Cent.	Remarks
Gm. per Liter of Urine, C	Gm. per 24 Hours, D	Gm. per Liter of Plasma					
		Calculated	Actual	Difference			
2.5	2.76	5.736	6.125	+0.389	6.009	59	Slight edema of legs; albumin = 4 gm. per liter
4.56	7.20	5.84	6.562	+0.722	6.342	79	
3.5	3.27	5.763	6.50	+0.737	6.357	72	
3.87	4.06	5.783	5.875	+0.092	5.712	73	Albumin = 2 gm. per liter
3.37	5.49	5.804	5.843	+0.039	5.659	74	
4.81	9.23	5.879	5.906	+0.027	5.647	75	Albumin, a trace
4.12	17.97	5.966	6.200	+0.234	5.966		
5.68	15.40	5.968	5.812	−0.156	5.464	48	
7.18	6.19	5.853	5.937	+0.084	5.704	81	
9.93	14.53	6.006	6.062	+0.056	5.676	85	Discharged. Albumin a trace

TABLE 5.—The Diet Prescribed in Case 2 During the Study of the Kidney Excretions.

Date	Diet	Sodium Chlorid	Fluid Intake, C.c.
3/ 6/17	Restricted protein	Salt-free	1,500
3/14/17	Protein, 52; fat, 73; carbohydrate, 118	Salt free	1,500
3/20/17	Protein, 64; fat, 86; carbohydrate, 187	Salt-free	1,500
4/11/17	Protein, 80; fat, 90; carbohydrate, 250	Salt-free	1,500

Two nephritic test meals, one shortly after admission and one late in convalescence, are given in full. The second shows a marked impairment of function.

Blood: Dec. 5, 1916, the red blood cell count was 3,305,000, white blood cells, 7,000, and the hemoglobin was 55 per cent. (Sahli).

Urine: Dec. 4, 1916, the color was reddish amber; specific gravity 1.020, with 6 gm. of albumin per liter. Microscopically there were many red blood cells, granular and cellular casts.

Table 8 gives in full the urea and chlorid studies and the phenolsulphonephthalein tests.

TABLE 6.—Record of Results Following Nephritic Test Meals.

Case 2: March 8, 1917. Administered shortly after admission

Time of Day	Urine, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8-10	135	1.018				
10-12	155	1.017				
12- 2	190	1.016				
2- 4	135	1.015				
4- 6	168	1.016				
6- 8	185	1.015				
Total day	968	.....	0.26	2.52	0.886	8.50
Night, 8-8	720	1.018	0.22	1.58	0.992	7.04
Total 24 hours	1,688	.....	.....	4.10	.....	15.54
Intake	1,760	.....	.....	7.5	.....	13.4
Balance	+72	.....	.....	+3.4	.....	—2.14

Case 2: May 14, 1917. Administered late in convalescence

8-10	111	1.026				
10-12	112	1.023				
12- 2	145	1.018				
2- 4	171	1.016				
4- 6	116	1.020				
6- 8	118	1.023				
Total day	773	.....	0.72	5.56	0.63	4.90
Night, 8-8	740	1.018	0.62	4.62	0.62	4.59
Total 24 hours	1,513	.....	.....	10.20	.....	9.49
Intake	1,760	.....	.....	8.5	.....	13.4
Balance	+247	.....	.....	—1.70	.....	+3.91

DISCUSSION OF RESULTS

The first two cases may be grouped together, as they both show an involvement of the kidney's ability to eliminate nitrogen and chlorids, while the third may be considered to be a true chlorid case.

Case 1. Impairment in Rate of Urea Excretion with Convalescence. — In this case the main point that I wish to emphasize is the marked impairment in the rate of urea and of phenolsulphonephthalein excretion starting on December 1. Simultaneously the actual concentration of blood plasma chlorid and the level of the chlorid threshold show a return to practically normal figures. This prolonged extreme impairment in the rate of urea excretion first appeared at the time when the patient started to show marked improvement in the general clinical condition. From December 1 to January 13, clinically, he improved rapidly, his anemia disappeared, strength returned and hematuria rapidly subsided. The hematuria had completely disappeared by January 2, and the albuminuria, 8 gm. per liter at the onset, had dropped to a slight trace. At no time was there any serum globulin in the urine.

Case 2.—Steady Improvement in Function.—In contrast to the findings in Case 1 are those of Case 2, in which there was no slump in function, the rate of urea and of phthalein excretion improving from the onset. The general clinical condition of the patient ran parallel to the functional findings. On considering this point I believe that the marked and prolonged slump in function, as shown in Case 1, was due to a subsidence of the acute inflammatory condition present in the kidneys at the onset. Evidently, if an acute nephritis is severe enough, the function is hyperactive. As the inflammation subsides and the stimulation is removed the kidneys display a function which is more truly an index of the actual state of affairs. This is the critical period in any case of acute nephritis, as it is during this prolonged rest that great care must be taken not to overstrain the exhausted function. That this low level of function is often of much longer duration than supposed might be indicated by the results in Case 1.

In contrast to Case 1 are the findings in Case 2, in which there is no slump, but a steady improvement in function. This is explained, I believe, by the fact that the original inflammation was not severe enough to cause a hyperactive organ, rather the rate of urea excretion was in proportion to the disturbed process, and accordingly became a true index of the severity of the condition. Such would be the findings in the milder types of acute nephritis. Nevertheless, the function, as shown by the second test meal, has not improved to such an extent as the results in the rate of excretion of urea and of chlorids would indicate.

TABLE 7.—Record in Detail of the Studies Respecting Urea—

Case 3. Medical No. 24800—

Date	Weight, Kg.	Urine, per 24 Hours, C.c.	Urea				
			Gm. per Liter of Blood, Ur	Gm. per Liter of Urine, C	Gm. per 24 Hours D	McLean's Index	Ambard Constant
12/ 4/16	50.0	4,800	0.42	12.67	60.81	220	0.054
12/ 8/16	47.7	2,722	0.27	5.4	14.84	88	0.065
12/20/16	40.8	3,936	0.46	7.87	30.96	98	0.081
1/ 2/17	40.9	1,440	0.45	18.51	26.64	124	0.072
1/13/17	40.7	1,056	0.39	18.12	18.91	117	0.074
1/26/17	41.1	10,968	0.18	0.51	5.59	27	0.157
2/ 2/17	40.7	1,680	0.38	15.63	26.25	177	0.060
2/ 9/17	40.6	1,368	0.30	17.82	24.37	252	0.055
2/16/17	40.8	870	0.27	25.65	9.48	144	0.069
3/ 2/17	43.2	2,496	0.135	6.09	15.19	427	0.029
3/16/17	45.4	5,760	0.12	2.23	12.84	264	0.049
4/ 6/17	47.1	1,320	0.255	18.01	23.76	295	0.047
4/20/17	47.5	1,296	0.255	13.02	16.93	178	0.060
5/ 4/17	47.4	1,848	0.315	20.32	37.53	324	0.044
5/18/17	48.2	5,424	0.265	5.04	32.13	192	0.056
6/ 1/17	47.6	2,160	0.285	12.85	27.75	231	0.053
6/22/17	50.1	972	0.28	22.75	22.10	228	0.052
7/ 6/17	46.9	4,080	....	.....	.....	...	.....

—AND CHLORID EXCRETION AND THE PHENOLSULPHONEPHTHALEIN TESTS
—Diagnosis: Acute Nephritis

Sodium Chlorid					Threshold	Phenolsulphonephthalein, Two Hours, per Cent.	Remarks
Gm. per Liter of Urine, C	Gm. per 24 Hours, D	Gm. per Liter of Plasma					
		Calculated	Actual	Difference			
6.12	29.37	6.205	6.875	+0.67	6.29	36	Edematous
5.56	15.07	6.04	6.937	+0.897	6.517	..	Albumin = 6 gm. per liter
1.68	6.6	5.842	7.162	+1.320	6.940	81	
3.56	5.11	5.856	6.900	+1.044	6.664	81	
2.87	3.02	5.792	6.625	+0.833	6.452	..	Jan. 25, 1917, theophyllin, 15 grains
0.62	6.84	5.796	6.718	+0.922	6.542	..	Albumin = 2 gm. per liter
6.45	10.82	6.02	6.875	+0.855	6.475		
7.18	9.82	6.011	6.750	+0.739	6.350	..	Albumin = 0.5 gm. per liter
4.87	1.79	5.771	6.687	+0.916	6.586	85	Feb. 22, 1917, discharged
4.43	11.04	5.977	6.562	+0.585	6.205	74	
2.06	11.86	5.890	7.037	+1.147	6.767	89	Ate extra salt
6.62	9.73	5.974	6.625	+0.651	6.271	82	Albumin, heavy trace
7.13	9.24	5.970	5.969	−0.001	5.619	55	
2.68	4.95	5.821	6.062	+0.241	5.861	80	
2.12	11.52	5.907	6.062	+0.155	5.775		
3.37	7.29	5.877	5.812	−0.065	5.555	84	
6.0	3.83	5.880	5.625	−0.255	5.365	88	Albumin, a trace
1.3	5.30	5.775	5.437	−0.338	5.262	86	

TABLE 8.—Diet in Connection with the Observations Recorded in Table 7.

Date	Diet	Sodium Chlorid	Fluid Intake, C.c.
12/10/16	Protein, 61; fat, 85; carbohydrate, 127	Salt-free	1,500
12/17/16	Protein, 82; fat, 91; carbohydrate, 130	Salt-free	1,500
1/17/17	Low protein diet	Salt-free	1,500
1/27/17	Protein, 82; fat, 91; carbohydrate, 130	Salt-free	1,500
2/13/17	Protein, 79; fat, 119; carbohydrate, 149	Salt-free	1,500

The results of the study of one nephritic test meal carried out on admission is recorded in Table 9.

TABLE 9.—A Study of the Results Following a Nephritic Test Meal

Case 3: Dec. 4, 1916

Time of Day	Urine, C.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8-10, 10-12	192	1.019				
12- 2	190	1.019				
2- 4	105	1.020				
4- 6	129	1.020				
6- 8	140	1.019				
Total day	686	.....	0.60	4.08	1.00	6.86
Night, 8-8	375	1.018	0.58	2.14	0.85	3.14
Total 24 hours	1,061	.....	.....	6.22	.....	10.00
Intake	1,680	.....	.....	8.2	.....	9.4
Balance	+619	.....	.....	+1.98	.....	−0.6

Case 3. Functional Disturbances Confined to Excretion of Chlorids. — The third case is one in which the chlorid function is at fault and demonstrates rather well the possible duration of the disturbance even when on a salt-free diet, since it requires six months to bring the threshold to a normal level. Throughout, the rate of urea excretion was not impaired. The phenolsulphonephthalein, except for the first estimation on December 6, remained within normal limits.

Edema.—All three of the cases showed a moderate amount of edema on admission. This condition was most marked in Case 3. The edema disappeared long before the chlorid threshold had reached normal levels, but did not reappear when at a later date their levels became temporarily raised. Serum globulin failed to show in the urine in

Case 3, and the blood cholesterol remained normal, which would exclude it from the group of cases recently described by Epstein.[11]

Relation of Nephritis to Glucose Threshold.—The raised level of the glucose threshold present in many cases of acute nephritis is well shown in Case 1, in which, after 100 gm. of glucose were administered by mouth on a fasting stomach, the following results were recorded, November 8:

11:50 a. m.	0.100 per cent.	No glucose
12:00 noon	100 gm. glucose in black coffee	
1:00 p. m.	0.184 per cent.	No glucose
2:00 p. m.	0.217 per cent.	No glucose
3:00 p. m.	0.170 per cent.	Faintest trace
4:00 p. m.	0.111 per cent.	No glucose

On November 28 the test was repeated with the following results:

7:45 a. m.	0.090 per cent.	No glucose
8:00 a. m.	100 gm. glucose in black coffee	
9:00 a. m.	0.152 per cent.	No glucose
10:00 a. m.	0.156 per cent.	No glucose
11:00 a. m.	0.122 per cent.	No glucose
12:00 noon	0.120 per cent.	No glucose
2:00 p. m.	0.080 per cent.	No glucose

The foregoing results would indicate that the block for glucose was present only during the period of stimulation.

Action of Theophyllin.—There is another point which I wish to present. In Case 1, 15 grains of theophyllin (theocin) were administered by mouth January 9, which was followed by a very marked diuresis lasting for two days. Simultaneously with this diuresis the level of the chlorid threshold dropped to 5.342 gm. per liter, January 10, returning to 5.964 gm. per liter January 13. In Case 3, also, 15 grains of theophyllin were administered by mouth January 25, but there was no diuresis, and the chlorid threshold, January 26, was slightly raised to 6.542 gm. per liter. Simultaneously the McLean index fell from 117 to 27. This would indicate that in Case 3 the kidney failed to respond to the drug, accordingly showing an impairment of function rather than an improvement. Following up these suggestions I have tried the action of theophyllin on normal and pathologic kidneys with results that seem to indicate that the drug acts on the chlorid threshold, allowing the chlorids to pass out of the blood stream, as well shown in Case 1 in which the blood plasma chlorid dropped from 6.50 to 5.47 gm. per liter, the water following.

In no case in which diuresis was not obtained was there a lowering of the chlorid threshold. Usually when there was no diuresis the chlorid threshold became markedly raised and the rate of urea excretion impaired. This is well shown in a chlorid case of chronic nephritis

11. Epstein: Tr. A. M. A., June, 1917.

(Med. No. 25180) in which there was no diuresis, the chlorid threshold going from 6.114 to 6.640 gm. per liter, with a drop in the rate of urea excretion from 212 to 6.9 (McLean's index). Further observations are being conducted on the action of theophyllin which will be reported at a subsequent date.

SUMMARY

Studies have been conducted on three cases of acute nephritis which demonstrate the following points:

1. In very severe cases of acute nephritis the kidney function during the early stages is much better than the actual state of the kidneys would seem to warrant. This is due to the increased stimulation from which they are suffering.

2. With the subsidence of the inflammation the function tends to fall to a very low level, which level is more truly an index of the kidney state. As convalescence is established this level tends to return to that at which the kidneys remain permanently damaged. This "slump" in function takes place simultaneously with a marked improvement in the clinical condition of the patient.

3. Theophyllin probably acts in part by lowering the chlorid threshold, thereby allowing the chlorids to pass out of the blood plasma, water following.

I should like to express my thanks to Miss Jacobson, my chemical technician, for her careful work in carrying out a large part of the chemical estimations.

A PAPILLARY CARCINOMA OF THE KIDNEY WITH METASTASIS IN THE BRAIN *

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The relative infrequency of papillary carcinoma of the kidney proper reported in the literature is emphasized by Wohl[1] in his description of a malignant papillary adenoma of the kidney. He says that his is the twelfth instance of such adenopapillary tumors appearing in the literature, but he probably has not included in this number a report by Eisenstaedt.[2] The latter emphasizes the rarity of carcinoma of the renal parenchyma proper, and reports a tumor which in its microscopic characters resembles closely the one to be described. It contained papillae having very little supporting tissue, each pierced centrally by a thin-walled vessel. Kretschmer and Moody[3] in 1914 reviewed the reports of such tumors and found ten recorded. They added another, making a total of eleven recorded at that time.

At a necropsy performed by me for the purpose of establishing the cause of death, a soft fleshy tumor was found in the left kidney and a large tumor thrombus projected into the corresponding vein. In addition, there was noted another tumor, definitely metastatic, in the anterior pole of the left temporal lobe of the brain. The circumstances attending the illness of the deceased could not be obtained with any degree of certainty or detail.

History.—The patient was an adult 58 years and 6 months of age, a shipping clerk employed by a lumber company, who had been admitted to a hospital about eight weeks before his death with a history of having suffered a skull injury, the severity of which was not definitely known or determined. At the time of his admission to the hospital he presented some disturbances in mentality, which, associated with the foregoing history of an injury, led the attending physician to diagnose a brain injury, and to trephine the calvarium. About ten days after the first operation, a second exploration of the cranium was made and the original opening in the skull enlarged. Two urine examinations made during the patient's stay in the hospital were reported as showing no blood or albumin. The patient's condition was not improved by the surgical treatment and he gradually grew worse mentally, finally dying in a state of apathy and emaciation. The presence of a tumor of the brain was not considered during the

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* From the Department of Pathology, University of Chicago.

1. Wohl, M. G.: Malignant Papillary Adenoma of the Kidney, Surg., Gynec. and Obst., 1917, **24,** 61.

2. Eisenstaedt, J. S.: Primary Adenocarcinoma of the Kidney, Urol. and Cutan. Rev., 1916, **20,** 61.

3. Kretschmer, H. L., and Moody, A. M.: Malignant Papillary Cystadenoma of the Kidney with Metastases, Surg., Gynec. and Obst., 1914, **19,** 766.

clinical course of the disease. The important anatomic findings noted during the necropsy concern chiefly the left kidney and the brain, there being no other metastases observed, except about a half dozen grayish-brown nodules, the largest 2 mm. in diameter, scattered in the lung substance.

Postmortem Examination.—The left kidney was of about normal size (Fig 1). The renal vein was widely dilated by a tumor thrombus involving chiefly the two lowest branches of this vessel. It projected bluntly into the lumen of the vein almost completely occluding it, and was 2 cm. wide, 1.8 cm. thick and 4 cm. long. In the posterior portion of the lower pole of the kidney proper was a very soft, fleshy tumor, irregularly outlined, about 4 cm. by 4.5 cm. in its maximum surface dimensions. The kidney capsule over this area bulged slightly. The tumor itself was gray, and so soft that only after hardening in 10 per cent. formaldehyd solution was examination possible. On the transversely sectioned surfaces of the posterior half of the bisected kidney the tumor tissue appeared as a continuous gray zone of a maximum width of 1 cm., lying between the cortex and medulla. Its outline was irregular, but, in spite of its relatively small size, it had invaded extensively the venous blood system as the latter approached the pelvis of the kidney (Fig 2). In general the cortex of the kidney was involved to a greater extent than the medullary portion. Careful examination of the renal pelvis and the ureter, as well as the left adrenal, disclosed no gross alterations of these structures.

In the anterior pole of the left temporal lobe of the brain there was a reddish-brown area, irregularly round, 3.5 cm. in its surface diameter, roughened, and not sharply demarcated from the surrounding brain tissue (Fig 3). The dura immediately covering this area was adherent, and had been invaded but not penetrated by tissue arising from the area mentioned. There were no other striking changes on the outside of the brain except a slight opacity of the lepto
opposite the site of the decompression operation. Sections of the brain made after hardening demonstrated a rather extensive involvement of the anterior portion of the left temporal lobe. The maximum vertical and transverse dimensions were 3 and 4 cm., and the same anteroposterior dimension was 4 cm. The sectioned surfaces of the tumor were reddish-brown, consisting of gray areas of tumor tissue from 1 to 6 mm. in width scattered with irregularly sized and located areas of necrosis and liquefaction. Toward the posterior limits of the tumor and approaching the lateral ventricle on that side was a cyst 2 cm. by 2 cm. by 4 cm. filled with a limpid, brown fluid. Its posterior limit was opposite approximately the same part of the basal ganglia, and lay immediately outside and above the lateral ventricle. The tumor was clearly demarcated, but not encapsulated, merging without interruption into the surrounding brain tissue. In consistency its tissue was very soft and friable. There was some compression of the left lateral ventricle and displacement to the right of the brain tissue medial to the left lateral ventricle.

Microscopic Examination.—Histologic sections of the kidney showed a fairly constant structure (Fig 4). The tissue was cellular, with only a little supporting stroma. The tumor cells were about the diameter of polymorphonuclear leukocytes, their nuclei being granular, indented, oval or round, occupying about two-thirds of the entire cell, the cytoplasm staining a light pink with eosin. A rather striking feature microscopically was the radial arrangement of these cells about thin-walled, clearly defined capillaries, forming rosette-like structures about, or slightly larger than, the diameter of a normal kidney glomerulus, the center of such a structure being the cross section of a capillary. Usually the width of a rosette was about ten to fifteen cells, although larger and smaller ones were also present. From the periphery of the capillaries a delicate connective tissue stroma extended outward a short distance as narrow papillae covered by epithelium, the latter somewhat broken and disarranged by the manipulation and fixation of the tissues, but usually two to three cells in depth, the marginal portion of the rosette consisting chiefly of epithelial cells without

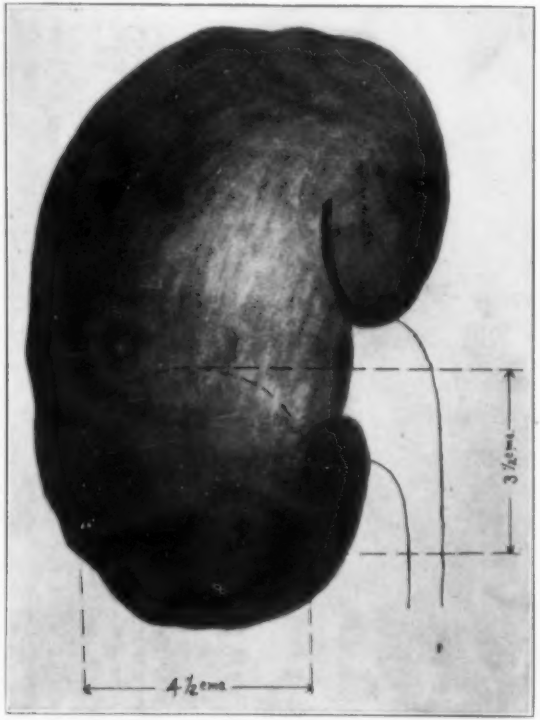

Fig. 1.—Drawing locating the primary tumor in the kidney.

Fig. 2.—Sketch representing the tumor thrombus in the left renal vein.

stroma (Fig. 5). This arrangement of the tissue cells was best understood after a serial section study by which the relation of the blood vessels and stroma to the epithelium could be determined. Such a study revealed a papillomatous structure, the thin-walled vessel of the rosette occupying the center of a villus, from which secondary radiating prolongations extended outward. At the extreme upper limit of the papilloma stem proper only cross sections of cells with a little stroma not constantly present were noted. Tangential sections of such papillae give the impression of rampant cell growth without definite

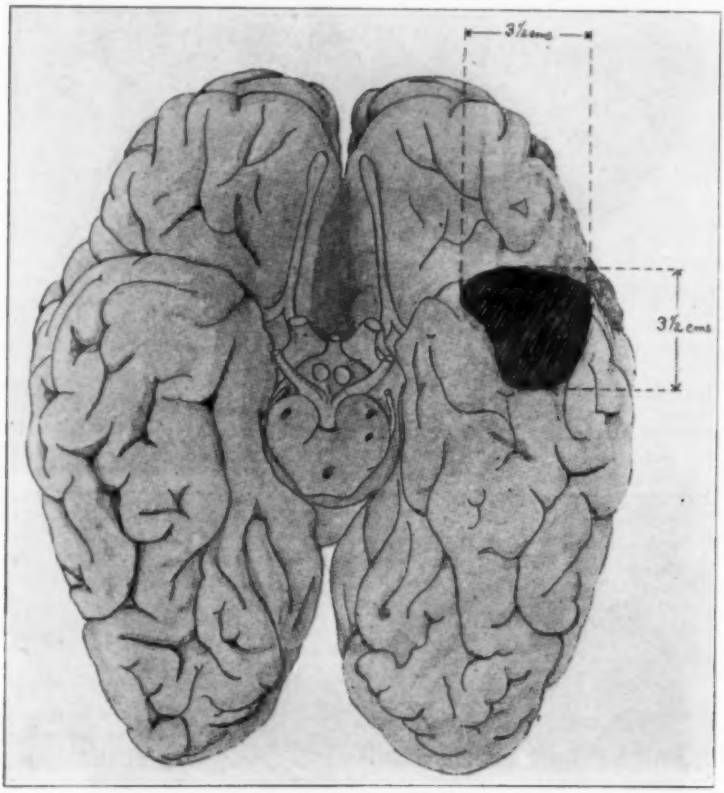

Fig. 3.—Diagrammatic sketch to locate the brain metastasis.

arrangement, excepting for the slight grouping of cells into clusters of three or five which might be interpreted incorrectly, except after a serial section study.[4] These areas were present in the tissues where the rosette structures were not definite, and had maximum dimensions varying between 0.5 and 1.5 mm. Irregularly scattered throughout the tumor substance were necrotic areas, into some of which hemorrhage had occurred. The necrosed tissues lay between

4. Le Count, E. R.: The Genesis of Carcinoma of the Fallopian Tube, Etc., Bull. Johns Hopkins Hospital, 1901, **12**, 55.

Fig. 4.—Photomicrograph illustrating the rosettes and papillae (×70).

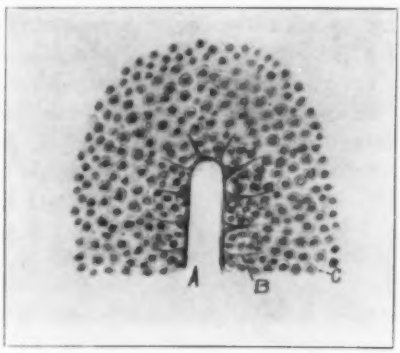

Fig. 5.—Diagrammatic sketch illustrating the structure of the papillary buds. *A*, thin-walled vessel in papilloma stem; *B*, stroma; *C*, tumor cells.

the peripheries of the papillae, corresponding therefore with the outer margin of the rosettes. In sections they varied from those just discernible to others as large as a rosette. The kidney substance in the region of the tumor was completely destroyed, while at the tumor edge the cells of the latter invaded the renal tissue, forming the structures described. Certain groups of tumor cells were pigmented brown by the split products of the red blood cells that escaped from the blood vessels with the necrosis of the tumor tissue.

Sections of the brain tumor showed a histologic structure similar in most respects to the tumor described in the kidney. The cells were identical in appearance, and for the most part had a radial arrangement about well defined capillaries, forming rosettes as in the kidney. Other areas of these cells, not so arranged, approximated 1 cm. in diameter, while between the peripheral margins of adjacent areas were equally extensive regions of tissue necrosis, with only remnants of nuclei and cell structure remaining. Some of these necrotic areas were from 2 to 3 mm. in their maximum dimensions, and involved not only the tumor proper, but also regions of brain substance. At the periphery of the tumor the growth of the tumor cells along the lymphatics might be noted where they appeared as small groups about the vessels, gradually encroaching on the brain tissue, causing its destruction and forming structures as heretofore described.

This tumor, without doubt, was primary in the left kidney, and, classified according to the description, belongs to the malignant papillary tumors arising in the renal parenchyma. Its early tendency to invade the blood vascular system is striking, and because of this its metastasis into the brain tissue is readily understood. The absence of well developed metastases in other organs, however, especially the lungs, is of interest, particularly when the entire clinical picture is considered from a diagnostic standpoint. The absence of positive urinary findings need not be taken seriously, especially since only two were reported during the eight weeks the deceased was under observation, and in all probability blood cells were present in the urine at some time during this interval. In conclusion, emphasis may be placed rightly on the importance of thorough routine examination, both physical and laboratory, with the hope that in so doing accuracy in diagnosing such tumors clinically may be approximated.

THE RELATIONSHIP OF THE TOXIC LYMPHOID HYPERPLASIAS TO LYMPHOSARCOMA AND ALLIED DISEASES*

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The dominant function of the lymphoid tissues is to arrest foreign substances brought to them in suspension and to manufacture phagocytic cells for the blood and tissue spaces. In certain situations, notably the gastro-intestinal tract, the geographical intimacy between the lymphoid tissues and an absorptive surface of enormous dimensions would seem to indicate that the lymphoid cells were placed there primarily for purposes of filtration, restraining such foreign bodies as bacteria, and filtering their toxins. That the lymphoid depots in question are a source of supply of wandering phagocytes cannot, of course, be denied, but that this function is subsidiary appears to be indicated by the fact that, in lymphatic leukemia, which is essentially a disease of the lymphoid hemopoietic system, the gastro-intestinal lymphoid follicles escape altogether, or exhibit a negligible degree of hyperplasia. The regional lymph nodes, on the contrary, such as those of the neck, axilla and groin, are actively engaged in both directions; that is to say, in the process of filtration and in the formation of lymphocytic phagocytes.

In addition to the lymphoid depots mentioned, there is an auxiliary system to be found in the form of small islands of lymphoid cells of rather wide distribution in the interstitial tissues of the thyroid, prostate, testicle, lungs, kidneys, liver and adrenal, in the subcutaneous tissues and serous membranes, and elsewhere. These deposits are sometimes so small as to escape notice in the routine histologic examination of tissues, at other times they are provided with definite germinal follicles and are easily seen. One is, nevertheless, apt to receive the impression that these lymphoid foci are functionally insignificant, and doubtless this is true. They are, however, not infrequently brought into prominence in certain diseases characterized by hyperplasia of lymphoid cells, particularly in Hodgkin's disease and lymphosarcoma, while in the liver in enteric fever they undergo increase in size in com-

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* From the Pathological Laboratories of Bellevue Hospital, Director: Dr. Charles Norris.

pany with the intestinal, mesenteric and splenic follicles, giving rise to the so-called focal necroses. In lymphatic leukemia they seldom share in the process of hyperplasia.

The spleen appears to occupy the same relationship to the arterial blood as the lymph nodes bear to the skin and mucous membranes. The presence of lymphoid follicles in the spleen and their close connection with its vascular supply, is of itself an indication that, among other things, the organ is part of the body's filtration plant. Other facts lend color to the view. Thus, the frequent occurrence of sclerotic and degenerative changes in the splenic artery suggests that this vessel is engaged in the transportation of vitiated blood to the splenic substance, while the absence of corresponding changes in the splenic vein indicates that its blood has been partially purified in the spleen before being expelled and subjected to further detoxication in the liver.

In addition, the spleen is a favorite site for separating bacteria and other parasites from the circulation, as shown by the experimental bacteremias,[1] and in the same way, it is sometimes possible to demonstrate malarial parasites in scrapings or sections from the splenic pulp after repeated examinations of the peripheral blood have failed to show them. Still further confirmation is to be found in the presence of sclerotic infarctions in the spleen associated with healed or healing infective lesions of the heart valves, in which circumstances bacteria are transported during the active periods of infection from the endocardium to the splenic vessels where, acting primarily on the intima, they produce infective lesions characterized by thrombophlebitis and infarction.

Moreover, the histology of the spleen is peculiarly adapted to purposes of filtration, the distensible sinuses lending themselves admirably to the temporary pooling of blood, so that the blood itself or the endothelial cells of the sinuses, or both, may deliberately exert lytic properties on alien cells deposited in the spleen. Thus, metastasizing tumors rarely find hospitable lodgment in the spleen, even in those cases in which dissemination of tumor cells by the lymph or blood stream produces secondary growths in practically every other organ in the body. Of 298 malignant tumors studied by myself at Bellevue Hospital,[2] the spleen was metastasized sixteen times, or in 5.3 per cent., and in practically every instance the secondary growths were small in both size and number. In a single exception the spleen was riddled by metastases following neoplasmic thrombosis of the splenic vein and retrograde embolism to the venous sinuses. In five cases of generalized tumor metastases the spleen was involved but once — a case of melano-

1. Bartlett and Ozarki: Jour. Med. Research, 1917, **35**, 465.
2. Symmers, D.: Am. Jour. Med. Sc., 1917, **154**, 2255.

matosis in which there were three secondary deposits — and yet, in all of these cases, the spleen must have been visited on innumerable occasions by tumor cells whose vegetative properties were no less exalted than in those which were delivered to and successfully inoculated in other tissues.

Finally, it may be recalled that, in disturbances of the bone marrow, such as occur in myelogenous leukemia and Hodgkin's disease, fully formed myeloplaxes are not uncommonly discharged into the circulation and separated out in the splenic sinuses, a finding which has also been observed in experimental infection of certain lower animals by the bacillus of hog cholera, pyocyaneus and anthrax, and after repeated artificial hemorrhages.[3]

THE REACTION OF THE LYMPH NODES TO IRRITATION

The lymph nodes are called on to deal with at least two varieties of extraneous material, namely, solid particles, such as coal dust and other pigments, the bodies of bacteria, cell débris and the like, and soluble irritants in the form of toxins derived from the skin and mucous membranes or formed in the lymph nodes by living micro-organisms. The cellular reactions in the lymph nodes vary according to the nature of the foreign bodies offered to them for disposal. In the case of insoluble particles, such as coal dust, the reaction consists in fibrotic changes in the interstitial framework, usually with, but sometimes without, corresponding numerical increase in the endothelial cells of the sinuses. The lymphoid cells maintain a passive attitude, but, as time goes on and the sinuses become occluded by desquamated endothelium and pigment granules, or are encroached on by the growing connective tissues, the flow of lymph is impeded and the lymphoid cells suffer atrophy and diminution in numbers.

In the case of bacteria the reaction in the lymph nodes differs with the nature of the invading parasite. For example, the typhoid bacillus, which combines with the bacillus of tuberculosis and the spirochete of syphilis to form a group of micro-organisms expressing an inimical predilection for lymphoid tissues, acts on the lymph nodes in such fashion as to produce necroses, together with hyperplasia of endothelium and of lymphoid cells. In the case of the tubercle bacillus, the most frequent change consists in the formation of tubercles, usually of the so-called epithelioid type, a reaction which is a deliberate attempt to limit the activity of a foreign body by erecting a structural barrier between it and healthy tissues. At the same time the lymphoid tissues in the immediate vicinity of the tubercle, or even throughout the node,

3. Opie: Am. Jour. Med. Sc., 1904, **126**, 988; Pugliese: Fortschr. d. Med., 1897, **15**, 727.

undergo hyperplasia, representing a response to the action of toxins derived from the bacillus — a type of biologic phenomenon the significance of which was first clearly recognized by Weigert[4] who, on the basis of observations of this sort, postulated the doctrine of regenerative over-production of cells. He advanced the view that physiologic structure and function depend on equilibrium maintained by the mutual restraint of cells, and that destruction of a cell or group of cells releases restraint to an extent sufficient to disturb the equilibrium of the remaining cells, in this way permitting them to exhibit abnormal proliferative energies and to produce new cells in abundant excess of those actually required to compensate for loss. Hyperplasia, therefore, is not a direct, but an indirect result of irritation, the irritant serving to destroy cells and not to stimulate those that remain in the direction of regeneration. The doctrine of regenerative overproduction finds a corollary in the process of paralytic and degenerative hypersecretion, which is of frequent occurrence in pathologic conditions. For example, section of the corda tympani nerve results in focal degeneration and necrosis of the nuclei of the submaxillary gland, and this, in turn, is followed by abundant hypersecretion of saliva. The same process is illustrated by various inflammatory reactions, notably the catarrhal lesions, which are attended by extensive degeneration of cells and by hypersecretion of mucus. Even in physiologic conditions the process of degenerative hypersecretion is sometimes to be observed, the overproduction of milk by the lactating breast being accompanied by destructive changes in the cells of the galactiferous tubules. It is apparent, therefore, that, in reacting to injury as well as in responding to physiologic demands, nature is apt to be prodigal not only of cells but of secretions as well.

Weigert's doctrine of overproduction is abundantly illustrated; in fact, examples are far too numerous to permit of more than passing mention at this time. Suffice it to recall the excessive regeneration of tubules in the lactating breast and in chronic interstitial mastitis, as well as in certain forms of adenomatoid hyperplasia of the thyroid, stomach, colon, prostate, liver and other organs. In all of these conditions not only is the supply of new cells greatly in excess of the number lost, but the new cells constitute a menace, since they approach a type of architecture in which equilibrium between structure and function is unstable, and, unless every source of irritation is removed, growth is apt to proceed beyond the control of the body and a malignant tumor result. The doctrine is likewise applicable to the lymphoid tissues, among which excessive regeneration of cells occurs in a variety of circumstances attended by the presence in the tissues

4. Weigert: Verhandl. d. Gesellsch. d. Deutsch. Naturforsch. u. Aerzte. Part 1, September, 1896, 121.

of toxic substances which act as irritants. Thus, the injection of tetanus toxin into the sciatic nerve is followed by hyperplasia of the lymph nodes in the vicinity of the nerve trunk, and, in certain non-ulcerative malignant growths, hyperplasia of the regional nodes is not infrequently demonstrable microscopically, due, undoubtedly, to the absorption of irritant products. In this connection, the experiments of Flexner[5] are of great significance. He has shown, for example, that the injection of lymphotoxins in geese and guinea-pigs, when carried out over a long period, is followed by extraordinary hyperplasia of the lymph nodes throughout the body.

Tuberculosis, however, furnishes the best examples of toxic lymphoid hyperplasia. There is a form of tuberculous lymphadenopathy consisting of diffuse hyperplasia of lymphoid cells without any suggestion of tubercles, the establishment of the nature of the process depending on the detection of tubercle bacilli in the enlarged nodes, on the experimental reproduction of tuberculosis in susceptible animals following the injection of emulsified tissues, or on comparison with preceding or subsequent lesions in the same type of tissue in the same individual. A case of this description occurred in a 6-year-old boy at the New York Hospital. The patient presented an enormous mass on one side of the neck. Removal and microscopic examination of the enlarged nodes showed tubercles in practically all of them. Several months later the nodes on the opposite side became enlarged following an attack of diphtheria. In these the only detectable change consisted in extensive and diffuse hyperplasia of lymphoid cells. Neither tubercles nor tubercle bacilli were found in spite of an exhaustive attempt to learn the nature of the lesion, and whether it was a form of tuberculosis, or whether it was due to the absorption of toxic products from the diphtheritic membrane, was never satisfactorily determined.

It is interesting to observe that tuberculosis is held to be responsible for a certain percentage of all cases of hyperplastic tonsillitis, a view which has been challenged by certain observers on the basis of failure to find tubercles in the enlarged tonsils. In guinea-pigs, however, it has been found that injection into the tonsil of given strains of tubercle bacilli results in marked lymphoid hyperplasia, not alone in the tonsils, but in the regional nodes, and this without the formation of tubercles in either locality, tubercle bacilli, however, being demonstrable, by appropriate methods of staining, weeks or even months later. It follows, I think, that certain cases of apparently simple hyperplastic tonsillitis in human beings might be ascribed to the same cause.

5. Flexner: Univ. Penn. Med. Bull., 1902, **15**, 287.

Finally, there is a variety of disseminated lymphoid hyperplasia[6] of tuberculous origin characterized by involvement of the lymph nodes throughout the body and by participation of the lymphoid structures of the stomach and spleen without the occurrence of tubercles in any of the localities named.

In connection with the same general subject I may cite the case of a woman, 55 years of age, who, about a year prior to this report presented a mass on the right side of the neck that was about the size of an adult fist. The growth projected into the side of the mouth, displacing the tonsil backward. Both the skin and mucous membrane covering the mass were intact. A portion of the growth was removed and sent to me for microscopic examination. I returned a diagnosis of lymphosarcoma, based partly on the microscopic appearances and partly on the fact that Gram-Weigert and Levaditi preparations and sections stained by Hermann's method for tubercle bacilli were negative. The patient was regarded by the surgeon as inoperable, and she was subjected to treatment by radium. The growth disappeared completely. In the light of this astonishing result I submitted the original microscopic preparations to two disinterested pathologists, both of whom concurred in the diagnosis of lymphosarcoma. Whether the diagnosis was correct or not, however, is largely a matter of scientific interest, and does not modify the fact that the mass was a localized lymphoid hyperplasia, apparently of toxic origin, the cells growing with such rapidity as to jeopardize life.

LYMPHOSARCOMA

In the necropsy service at Bellevue Hospital in the past ten years there have been twelve cases of lymphosarcoma, which, taking into account the fact that our necropsy records exceed 5,500, indicates that the lesion is not a common one. Eleven of the twelve cases occurred in males. In six of the cases the growth was first observed in the cervical lymph nodes; in three the changes observed postmortem suggested that the process commenced in the lymphoid remains of the thymus gland, and the remaining three in the small intestine. Some of the cases exhibited features which are considered worthy of presentation at length.

Lymphosarcoma is essentially a growth of regional distribution, although occasionally it displays an extraordinary faculty for bringing about diffuse lymphocytic infiltration of remote viscera. At other times it is associated with variable numbers of lymphoid nodules in such organs as the kidney, liver and suprarenal capsule where, in normal conditions, lymphoid cells are present only in the form

6. Coley and Ewing: Proc. New York Path. Soc., New Series, 1909, **10**, 145.

of foci so minute as scarcely to attract notice on microscopic examination. To the unaided eye these nodular "metastases" in lymphosarcoma appear to be well circumscribed, but, on microscopic examination they fade into the surrounding tissue spaces in such gradual fashion as to indicate hyperplasia of pre-existing lymphomas rather than foci springing from transplanted cells derived from a remote growth.

Anatomically, the lymphosarcomas are divisible into five groups, one (*a*) characterized by diffuse infiltration of tissues, more especially of paired organs; a second, (*b*) involving regional collections of superficial lymph nodes; a third, (*c*) implicating the lymphoid structures of the thorax, notably the remnants of the thymus gland and the lymph nodes at the root of the lung; a fourth, (*d*) the lymphoid tissues of the abdomen, including the stomach, intestine, spleen and lymph nodes, and, fifth, (*e*) there is a variety of leukosarcoma, described by Sternberg, which is characterized by lymphoid tumors in unusual situations, the growth pouring its lymphocytes into the blood in such quantities as to constitute a leukemia. In this category belongs, also, I believe, the disease commonly known as chronic lymphatic leukemia.

SYMMETRICAL LYMPHOSARCOMA

(*a*). *Mikulicz' Disease.*—The implication of paired organs by lymphosarcoma is well shown by a lesion first fully described by Mikulicz. It usually commences as an infiltrative overgrowth of the lymphoid cells normally existing in the stroma of the lacrimal glands, and is manifested by symmetrical enlargement of the outer two-thirds of the upper eyelids, followed by symmetrical enlargement of the parotid and submaxillary glands. In the case originally described by Mikulicz the histologic changes were characteristic of lymphosarcoma, small collections of closely packed lymphoid cells being supported by delicate trabeculae of connective tissue. Precisely the same combination of symmetrical lacrimal, parotid and submaxillary adenopathy has since been observed in lymphatic leukemia, the change depending on diffuse infiltration of lymphocytes.

(*b*). *Symmetrical Conjunctival Lymphosarcoma.* — A condition related to Mikulicz' disease is to be found in bilateral lymphosarcoma of the conjunctival lymphoid follicles — a lesion which does not appear to have been described previously. The case which came under my observation was that of a man, 37 years of age. The palpebral conjunctiva of the right eye was greatly swollen and thrown into folds which caused eversion and depression of the lower lid and encroached on the ocular conjunctiva to the lower level of the cornea. The conjunctiva of the opposite eye was similarly affected, but to a less extent.

Microscopic examination revealed the histologic picture of lymphosarcoma with neoplasmic infiltration of the tissues of the lid.

(*c*). *Symmetrical Lymphosarcoma of the Paired Viscera.* — The tendency of lymphosarcoma to bring about symmetrical neoplasmic infiltration of certain tissues is shown by bilateral invasion of the mammae, ovaries, testicles, suprarenal capsules and certain paired members of the bony system — a remarkable capacity which it shares with the so-called chronic lymphatic leukemia and its alleged companion lesion, pseudoleukemia.[7] One of the most striking of all the symmetrical infiltrations in lymphosarcoma, however, is to be seen in the kidneys, in which vast hordes of tumor cells penetrate the connective tissue framework and produce enormous enlargement of the organs without correspondingly extensive or severe microscopic alterations in the tubular epithelium or very profound disturbances in the excretory function of the kidney. Here, again, lymphosarcoma is not alone in producing changes of the sort described, since an identical lesion exists in the kidney in the so-called pseudoleukemia, having, in fact, been observed by Cohnheim in his original case.[8]

Three examples of symmetrical lymphosarcomatous infiltration of the kidneys occurred in the Bellevue Hospital necropsies, in two of which the original focus of growth was apparently in the lymphoid remains of the thymus gland, while the third was associated with lymphosarcoma of the small intestine. In the Bellevue cases the several clinical histories and necropsy protocols have been abbreviated as much as is consistent with an intelligible presentation, and are as follows:

CASE 1.—The patient was a man, aged 26, a butcher by trade, who was admitted to the hospital complaining of shortness of breath. He said that three weeks before admission he suddenly became short of breath and subject to a severe cough attended by pain in the chest and expectoration. On admission it was noted, in addition, that the fingers were cyanotic, that the subcutaneous tissues were edematous and that ascites was marked. Repeated examinations of the sputum for tubercle bacilli were negative. The temperature was normal throughout. The urine showed a trace of albumin and hyaline and granular casts. The blood contained 13,000 leukocytes, of which 34 per cent. were lymphocytes. Physical examination revealed slight bulging and dulness over the lower right side of the chest and dulness beneath the right infraclavicular region and between the scapulae. The area of cardiac dulness was increased, the apex beat was neither visible nor palpable and the heart sounds were muffled.

Necropsy (1483).—The body was that of a man, 26 years of age. On section the subcutaneous tissues were universally edematous. The peritoneum was thickened and opaque and enclosed several liters of turbid, yellowish fluid. On removing the sternum the anterior mediastinum was found to be occupied by a growth which, in a general way, conformed to the shape of the thymus gland, and measured 9 by 13 by 10 cm. The mass extended downward as far as the level of the auriculoventricular groove and upward to within a short

7. Fabian: Beitr. z. path. Anat. u. allg. Path., 1912, **53,** 491.
8. Cohnheim: Virchows Arch. f. path. Anat., 1865, **33,** 451.

distance of the lower border of the thyroid gland. Laterally it infringed on the root of the left lung, bands of tumor tissue infiltrating the connective tissue planes along the larger bronchi for a distance of several centimeters. On section, the growth was made up of yellowish white tissue which was divided into lobules of variable size by bands of dense, whitish connective tissue. The substernal, peribronchial, peritracheal and lower cervical lymphnodes were enlarged, discrete, the largest approximating the size of a cherry, and, on section, the cut surface was bulging.

Heart: The pericardium contained about 200 c.c. of turbid, yellowish fluid with fibrin flocculi, and both layers were covered by fibrinous exudate. The heart was greatly increased in size and the epicardial fat was diffusely infiltrated by grayish yellow tissue similar to that of the growth in the region of the thymus gland. The walls of both ventricles were enormously thickened, rigid, and largely replaced by grayish yellow tumor tissue, islands of reddish musculature being preserved at scattered intervals. The pleura covering the parietal and diaphragmatic surfaces of the right lung measured 0.5 cm. in thickness and was adherent to the chest wall, pericardium, and diaphragm through the medium of infiltrated tumor tissue.

Kidneys: The kidneys were massively enlarged and weighed together 1,300 gm. Each measured 17 by 8.5 by 8 cm. The cortices were unusually broad and grayish yellow in color, standing out in marked contrast to the dark red pyramids. On section the cut surface was smooth, pale, the substance bulging and glazed. The mesenteric and retroperitoneal nodes were enlarged to the extent of from 1 to 4 cm.

Anatomic Diagnosis.—Lymphosarcoma of the anterior mediastinum corresponding to the lymphoid remains of the thymus gland; lymphosarcomatous infiltration of the peribronchial connective tissues of the left lung and of the parietal pleura of the right lung, of the pericardium and both ventricles of the heart; serofibrinous pericarditis; massive symmetrical lymphosarcomatous infiltration of the kidneys; lymphosarcomatous hyperplasia of the substernal, peritracheal, peribronchial, lower cervical, mesenteric and retroperitoneal lymph nodes.

Microscopic Findings.—Microscopic examination of the growth in the region of the thymus showed the presence of innumerable large and small islands of lymphocytes separated by irregularly distributed bands of fibrous tissue. The lymphocytes in the islands showed no arrangement comparable to the delicate alveolar network so frequently seen in lymphosarcoma, but were closely packed in sheetlike arrangement. The connective tissue planes of the heart were richly infiltrated by tumor cells, the intervening muscle fibers being atrophied or completely destroyed and replaced by broad sweeps of lymphocytic cells. The connective tissues of the cortex of the kidneys were invaded to an extraordinary degree by lymphocytes, the tubules being widely separated and the glomeruli surrounded. The tubular epithelium was granular and swollen. The medulla was free. The architecture of the lymph nodes was completely lost and replaced by dense, diffusely arranged lymphocytes which infiltrated the capsule and could be seen streaming off into the surrounding tissue spaces. The other viscera revealed no microscopic changes of note.

Case 2.—The patient was a boy, aged 17, who, on admission to the hospital, said that two weeks previously he suddenly became short of breath and was seized by dull, constant pain in the upper part of the chest, attended by cough and expectoration. The urine contained a trace of albumin, but no casts. Frequent examinations of the sputum for tubercle bacilli were negative. The sputum was blood tinged. Both legs were edematous and the face and neck were cyanotic. Physical examination of the chest showed marked flatness extending from the clavicles downward, and thoracentesis was attended by withdrawal of enormous amounts of blood tinged fluid. At this time the heart sounds were clear. The abdomen was distended by fluid.

Necropsy (2836).—The body was that of a boy, 17 years of age. The abdomen was prominent and, on section, released a large amount of faintly blood tinged fluid. Both lower extremities were edematous. On opening the thorax both pleural cavities were found to contain large quantities of slightly blood tinged fluid, compressing the lungs, which were displaced upward. Lying in the anterior mediastinum corresponding to the position of the thymus gland was a large, pale or yellowish, firm mass which extended upward as far as the lower level of the neck and downward in front of the pericardium to the level of the auriculoventricular groove.

Heart: The pericardium was distended by a large amount of bloody fluid. The parietal pericardium was thickened, and strewn over the visceral layer was a collection of reddish, shaggy, fibrinous exudate. The heart muscle in the upper part of the left ventricle was fleshy in appearance.

Kidneys: Both kidneys were increased in size, measuring 15 by 10 by 8 cm., weighing together 1,040 gm. The form was well preserved and the surface was extremely pale, the cortex broad, fleshy, and the markings obscured.

The retroperitoneal and lower cervical lymph nodes were slightly enlarged. The bone marrow presented numbers of scattered, whitish areas.

Anatomic Diagnosis.—Lymphosarcoma of the anterior mediastinum, corresponding to the region of the thymus gland; lymphosarcomatous infiltration of both kidneys; lymphosarcomatous hyperplasia of the cervical and retroperitoneal lymph nodes and of the pericardium and the superficial muscular planes of the left ventricle of the heart; hemorrhagic serofibrinous pericarditis; ascites; bilateral hydrothorax.

Microscopic Examination.—The histology of the growth found in the anterior mediastinum in the position of the thymus gland showed a scanty connective tissue framework of irregular distribution, in the meshes of which were enormous numbers of closely packed lymphoid cells. The architecture of the lymph nodes was entirely obscured by diffuse overgrowth of identical cells. The epicardium was covered by a thick layer made up of a superficial stratum of fibrin, below which was a quantity of richly vascularized granulation tissue densely sown with lymphoid cells. Below this, in turn, was a zone composed exclusively of lymphoid cells, running downward from which into the intramuscular planes of the heart was a rich infiltrate, which ceased, however, a few millimeters beneath the surface. The bone marrow was richly strewn with lymphocytes.

From the pathologic standpoint the two cases are interesting as emphasizing the occurrence of massive lymphosarcomas on the basis of the lymphoid remnants of the thymus gland, the growths giving rise, clinically, to detectable signs of intrathoracic pressure, including changes in the pericardium due to neoplasmic infiltration and embarrassment of the heart's action from a like cause. The massive symmetrical infiltration of the kidneys is likewise interesting, particularly in view of the few changes referable to the secretion of urine.

Case 3.—In a third case encountered at Bellevue Hospital the patient, a man, aged 56, was admitted with the classical signs of cardiac decompensation, death being due to croupous pneumonia. The urine contained a trace of albumin and a few hyaline and granular casts. Beyond this the clinical history contained nothing of interest in the present connection. At necropsy the middle of the jejunum presented two infiltrated, whitish elevations, 4 cm. in diameter that extended around the intestine in bracelet fashion. They were separated from one another by several centimeters of healthy mucosa. A similar circumferential infiltrated band, 1 cm. in diameter, was found in the

middle of the ileum, the center of the band, corresponding to the mesenteric attachment, being ulcerated.

Kidneys: The kidneys were enlarged and weighed together 630 gm. They were yellowish white and, on section, the cortices were broadened and the markings were obliterated by cream colored tissue. Numerous minute whitish specks were visible in the cortex.

Anatomic Diagnosis.—Lymphosarcoma of the small intestine; symmetrical infiltration of the adrenals and kidneys; lymphosarcomatous foci in the liver.

Microscopic Examination.—The histology of the growth in the intestine showed scattered areas of superficial ulceration and great thickening of the wall due to infiltrating lymphocytes. The kidneys displayed enormous numbers of lymphocytes invading the intertubular spaces from cortex to pelvis. The malpighian follicles and tubular epithelium appeared to be well preserved. In the liver were innumerable minute lymphocytic foci, most of them lying in the connective tissue at the periphery of the lobules. The adrenals revealed large numbers of lymphocytes arranged in islands or scattered diffusely through both cortex and medulla.

In all of the three cases just synopsized the kidneys exhibited remarkable increase in size due to infiltration of hordes of tumor cells in the connective tissue framework, with or without attendant granular changes in the epithelium of the convoluted tubules, while the urinary changes were insignificant. It is not at all clear why a lymphosarcoma in such a remote locality as the upper thorax, or even in the intestine, should bring about diffuse symmetrical invasion of one or more sets of organs in distant parts. The only possible explanation seems to me to be that, in these circumstances, tumor cells are displaced at intervals from the parent growth and filtered out as a result of the presence in the recipient tissues of a chemotactic force, since, in the very nature of things, it is hardly conceivable that the resident lymphomas could occasion such widespread hyperplasia. In expressing this predilection for the paired viscera the lymphosarcoma is not alone. The so-called Krukenberg tumor, which is a primary carcinomatous growth springing from the parietal cells of the fundus glands in the stomach, commonly causes diffuse symmetrical invasion of the ovaries, and the same selective action is true of certain tumors which metastasize the suprarenal capsules, while the kidneys themselves are occasionally the seat of symmetrical metastases from tumors of the connective tissue series other than the lymphosarcomas.

PSEUDOLEUKEMIA AND ALLIED CONDITIONS

Shortly after Virchow described lymphatic leukemia, Cohnheim[8] recorded a case which presented identical anatomic characteristics without changes in the blood, and for this disease he suggested the name of pseudoleukemia. The designation has since been misapplied in various quarters and employed synonymously with Hodgkin's disease, from which, however, pseudoleukemia is readily distinguished on microscopic

examination. In Cohnheim's case the patient was a man, aged 24, who suffered from anorexia, vomiting and repeated attacks of epistaxis. The leukocytes were diminished in number. At necropsy, in addition to enlargement of the cervical, inguinal and retroperitoneal lymph nodes, the spleen was found to be greatly enlarged, measuring 25 by 17 by 8 cm., and the pulp was richly infiltrated by lymphoid cells. The kidneys were also increased in size, measuring 17 by 6 by 5 cm., and were infiltrated by lymphoid cells from cortex to pelvis.

In addition to the variety of pseudoleukemia described by Cohnheim, a related lesion of the gastro-intestinal lymphoid structures has been recognized. As far as I have been able to learn, the gastro-intestinal form is rare, only twelve cases having been found in the literature to date.[9] The lesion is characterized by extraordinary hyperplasia of the gastro-intestinal lymphoid structures, myriads of enlarged follicles stretching from the cardiac end of the stomach to the anal margins, causing great thickening and rigidity throughout. The individual follicles vary in size, and are so closely packed as scarcely to exhibit a hair's breadth between them. The thoracic and superficial lymph nodes are usually involved, but not nearly in the same relative proportions as the follicles in the stomach and intestine. The abdominal nodes, however, are apt to show marked changes. The spleen is almost invariably enlarged, often approximating the splenomegaly of lymphatic leukemia. The lymphoid cells in the blood are normal or approximately so—a fact which permits instant differentiation between the true and the so-called pseudoleukemia. Anatomically, the gastro-intestinal lesion in question belies the title of pseudoleukemia to the extent that, in true lymphatic leukemia, the lymphoid structures of the gastro-intestinal tract rarely, if indeed they ever, undergo a degree of hyperplasia even remotely comparable to that just described. In fact, in nineteen cases of chronic lymphatic leukemia of which I have records, the gastro-intestinal lymphoid structures were practically unchanged.

In view of the extremely vague relationship of pseudoleukemia to lymphatic leukemia, and because of the anatomic distribution of the changes in the lymphoid apparatus in the so-called pseudoleukemia, and because of the fact that identical or related changes are encountered in the same situations in lymphosarcoma, I am of the opinion that pseudoleukemia should be discarded as a misleading and inappropriate designation, and that the lesion so named should be included among the lymphosarcomas.

9. Symmers, D.: THE ARCHIVES INT. MED., 1909, **4**, 218; Shoemaker: New York Med. Jour., Jan. 1, 1910.

Chronic Lymphatic Leukemia. — Chronic lymphatic leukemia is a disease of the lymphoid system characterized by widespread and practically simultaneous enlargement of certain groups of lymph nodes, notably those of the cervical and axillary regions, the peribronchial nodes, and the spleen. It is attended by enormous preponderance of lymphocytes in the blood, the cells being poured into the circulation from the hyperplastic lymph nodes, by the presence of huge numbers of infiltrating lymphocytes in the blood vessels and lymph spaces throughout the body, and by enlargement of the splenic follicles and diffuse infiltration of the pulp, the sinuses sometimes being so crowded with lymphocytes as to constitute lymphoid thrombi. How much of the latter is due to the formation of lymphoid cells in the splenic follicles and how much to deposition from the blood, is impossible to say. The liver is almost always greatly increased in size, its sinusoids are strewn with lymphocytes and circumscribed lymphocytic foci are present at frequent intervals. Finally, the bone marrow, which, in normal circumstances, is practically devoid of lymphocytic foci, is almost completely replaced, myriads of lymphocytes occupying the marrow spaces, choking and distending the capillaries. In a word, lymphatic leukemia is primarily a disease of the lymphoid system, and the blood stream, viscera, and bone marrow are secondarily infiltrated by cells identical with those encountered in the lymphosarcomas — all of which is in keeping with the conception of a primary neoplasm of the lymph nodes. Reasoning by analogy with generalized toxic lymphoid hyperplasia in tuberculosis, it appears to me that chronic lymphatic leukemia may well represent an autonomous process due to a self-perpetuating lymphotoxin origin, that it belongs to the category of lymphosarcomas, and is an example of the applicability of Weigert's doctrine of regenerative overproduction. The interpretation of lymphatic leukemia as a neoplasm attended by circulating metastases is substantiated by Sternberg's[10] leukosarcoma —a disease characterized by the presence of multiple lymphoid tumors, the cells of which are poured into the blood in such numbers as to constitute a true leukemia. It is also confirmed by Ellermann's[11] observation that definite lymphoid tumors not infrequently develop in different situations in chronic lymphatic leukemia in both man and fowl.

SUMMARY AND CONCLUSIONS

1. In view of the fact that one of the principal functions of the lymph nodes is that of a filter, it is reasonably to be assumed that, in a great variety of circumstances, the nodes are subjected to the destructive action of irritants, not only in the forms of solid bodies, such as

10. Sternberg: Beitr. z. path. Anat. u. Allg. Path., 1905, **37**, 437.
11. Ellermann: Jour. Am. Med. Assn., 1917, **69**, 500.

bacteria, but as soluble substances of many descriptions. In the case of bacteria, the reaction in the lymph nodes differs with the type of micro-organism and is shown by simple phagocytosis and by regenerative and necrotic lesions, including, in the case of the tubercle bacillus, definite attempts to limit the sphere of activity of the invading parasite by the interposition of a mechanical obstacle in the form of a tubercle. The reaction to soluble poisons is different, as shown, for example, by diffusion of the toxin of the tubercle bacillus, which is followed by hyperplasia of lymphoid cells, sometimes to a limited extent, at other times involving groups of lymph nodes, at still other times including practically all the lymphoid tissues of the body.

Since the lymphoid tissues are so frequently exposed to the action of bacterial toxins and irritants brought to them in solution from absorptive surfaces of vast extent, and since, in these circumstances, they so often display a definite tendency to respond to irritation by hyperplasia of their cellular constituents, I think it not improbable that a like reaction is to be held responsible for the inception of certain types of disease characterized by overgrowth of lymphoid cells, local or general. If the irritant is withdrawn after the lapse of a reasonable interval of activity the cellular reaction in the lymph node ceases and the hyperplastic process is withdrawn. If, however, the irritant continues to act it appears to be inevitable that the cellular response will also continue. Finally, a time is to be expected at which, either as a result of the activity of the same irritant, or, more probably, as the result of the formation of a self-perpetuating toxin in the lymph nodes concerned, the reaction is converted into a process characterized by indefinite hyperplasia.

In the absence of a better explanation, this, I think, is a not illogical method of accounting for the origin of the lymphosarcomas and for similar otherwise inexplicable lesions of the lymphoid system, including not only certain localized lymphoid hyperplasias, but chronic lymphatic leukemia, pseudoleukemia and the like.

2. Chronic lymphatic leukemia and its companion lesion, pseudoleukemia, together with the familiar examples of lymphosarcoma, present many clinical and anatomic changes in common. The histologic alterations are closely akin; in fact, in many instances, they are indistinguishable one from the other. It is simpler and more natural, I think, to correlate these lesions than it is to strain at the impractical and artificial task of attempting to separate them into clinical and anatomic entities. For this reason I prefer to group them, together with Mikulicz' disease and the symmetrical conjunctival lymphosarcoma herein described, under the general heading of lymphosarcoma, as follows:

1. Symmetrical superficial lymphosarcoma
   - (a) Mikulicz' disease
   - (b) Bilateral conjunctival lymphosarcoma
2. Leukemic lymphosarcoma
   - (a) Chronic lymphatic leukemia
   - (b) Sternberg's leukosarcoma
3. Regional lymphosarcoma
   - (a) Cervical, axillary, inguinal
   - (b) Thoracic
     - Thymic
     - Peribronchial
   - (c) Abdominal
     - Gastro-intestinal
     - Intestinal
     - Mesenteric, retroperitoneal
4. Generalized lymphosarcomatosis

I wish to acknowledge my indebtedness to Dr. Louis Shapiro of the intern staff of Bellevue Hospital for valuable assistance in abstracting a number of clinical facts from the hospital records.

CHEMICAL CHANGES IN THE BLOOD AND URINE IN PROGRESSIVE MUSCULAR DYSTROPHY, PROGRESSIVE MUSCULAR ATROPHY AND MYASTHENIA GRAVIS *

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In May, 1916, we[1] reported the following findings in a case of progressive muscular dystrophy: (1) low blood sugar; (2) low cholesterin content of the blood; (3) creatinuria; (4) a rise in the sugar content of the blood accompanied by a corresponding increase in muscular strength following treatment.

We now submit further data[2] regarding the first patient, and figures for the glucose and cholesterin content of the blood and the creatin content of the urine in other cases of progressive muscular dystrophy, in progressive muscular atrophy, in myasthenia gravis, and — as controls — in conditions not accompanied by myasthenia of any form.[3]

PERCENTAGE GLUCOSE IN THE BLOOD

Progressive Muscular Dystrophy:
(1) 0.064 (2) 0.068
(3) 0.080

Myasthenia Gravis:
(4) 0.0818 (5) 0.095

Progressive Muscular Atrophy:
(6) 0.111 (7) 0.129

Chronic Arthritis:
(8) 0.086 (9) 0.088
(10) 0.090 (11) 0.098
(12) 0.101 (13) 0.103
(14) 0.104 (15) 0.106
(16) 0.109 (17) 0.115
(18) 0.118 (19) 0.121
(20) 0.124 (21) 0.128
(22) 0.131 (23) 0.166

Chronic Endocarditis:
(24) 0.103 (25) 0.105
(26) 0.107 (27) 0.110
(28) 0.127

Conditions Accompanied by Nephritis:
(29) 0.123 (30) 0.123
(31) 0.133 (32) 0.146
(33) 0.159 (34) 0.204

Miscellaneous Conditions:
(35) Hypertension 0.120
(36) Multiple sclerosis.. 0.110
(37) Hypotension ..... 0.144†
(38) Tumor of the cord. 0.140
(39) Psoriasis 0.090
(40) Tuberculosis of the spine 0.103
(41) Neoplasm 0.118
(42) Pernicious vomiting 0.094

Normal:
(43) 0.115 (44) 0.129

Chronic Arthritis with Rapid Muscular Wasting:‡
(45) 0.119 (46) 0.120

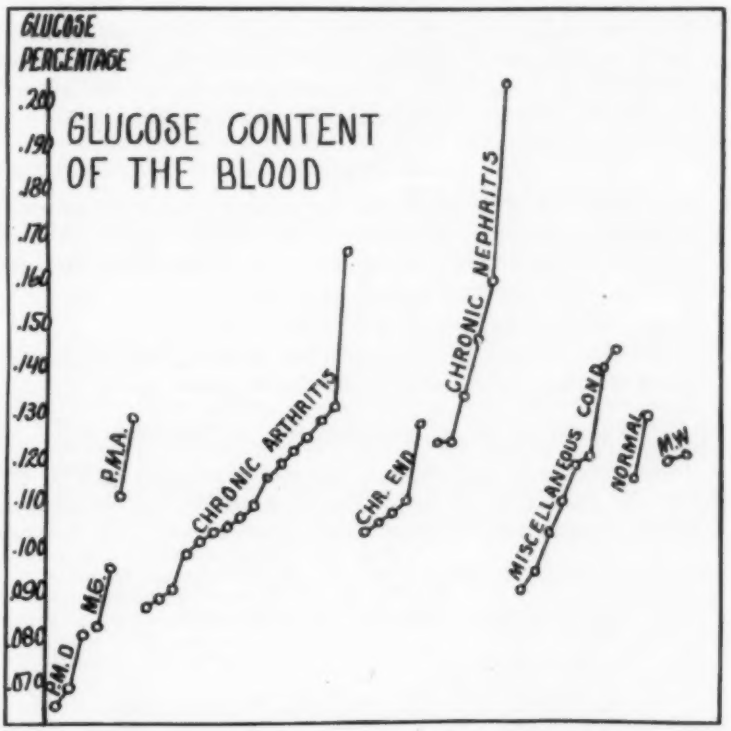
* Submitted for publication Oct. 23, 1917.
* From the Robert B. Brigham Hospital.

† In view of the fact that the epinephrin content of the blood is high in cases of hypotension (Bedford, E., and Jackson, H.: The Epinephrin Content of the Blood in Conditions of Low Blood Pressure and "Shock," Proc. Soc. Exper. Med. and Biol., 1916, **13,** 85), this low blood sugar, nearly high enough to give rise to glycosuria, is to be noted.

‡ These are the same two cases reported in the earlier paper in which myasthenia developed as the result of marked muscular wasting secondary to rapidly progressing chronic arthritis.

BLOOD SUGAR

The blood sugar in these cases (nephritis, progressive muscular dystrophy and myasthenia gravis excepted) falls between 0.09 and 0.13 per cent.[6] Since but few of these patients were in good health, the figures are not offered as normal standards; but other investigators have found approximately the same range of values in normal cases.[7]



Glucose content of the blood. Each small circle indicates glucose content of the blood in one case. Values for the same kind of disease are connected together with a line. Abbreviations P. M. D. = progressive muscular dystrophy; P. M. A. = progressive muscular atrophy; M. G. = myasthenia gravis; Chr. End. = chronic endocarditis; M. W. = cases of chronic arthritis with muscular wasting.

In the three cases of progressive muscular dystrophy the blood sugar is below the normal. In the two cases of myasthenia gravis the blood sugar is a little below the normal. In the two cases of progressive muscular atrophy blood sugar is normal.

CREATINURIA

Large quantities of creatin were present[5] in the urine of the two patients with progressive muscular dystrophy. The urine of the third (an outpatient) was not examined. In Patient 1 the creatin excretion ran from 0.283 to 0.624 gm. per day, the average for seven days being 0.465 gm. In Patient 2, creatin ran from 0.356 to 0.608 gm., the average for eleven days being 0.503 gm. per day.

Of the two patients with progressive muscular atrophy, one showed 0.198 gm. in a day's urine, the other an average of 0.130 gm. per day.

In one of the patients with myasthenia gravis (Patient 5) creatin was absent from the urine (the urine was examined every day for ten days). In the other (an outpatient) the urine was not examined.

CHOLESTERIN

The cholesterin of the blood was low in all three cases of progressive muscular dystrophy. The normal amount by the same method of analysis runs from 1.60 to 2.40 mg. per gram of blood, and averages about 1.90. The percentage in these cases was:

Case 1, 0.50 to 1.44; Case 2, 1.18; Case 3, 1.40.

Blood cholesterin was not low in the patients with progressive muscular atrophy or in those with myasthenia gravis.

BLOOD SUGAR AND IMPROVEMENT IN STRENGTH

In only one of the patients were we able to compare for long the glucose and cholesterin content of the blood with the improvement in muscular strength under treatment. The blood sugar was as follows:

	Blood Sugar Percentage
Oct. 27, 1915	0.068
Nov. 5, 1915	0.060
Treatment Begun	
Nov. 16, 1915	0.074
Nov. 23, 1915	0.091
Nov. 30, 1915	0.081
Feb. 21, 1916	0.095
June 20, 1916	0.110
March 7, 1917	0.103

From the time treatment began the glucose showed an almost continuous rise. There was a corresponding continuous gain in strength, and at the time of the last examination the patient had nearly completely regained his strength. Under treatment for ten days the blood sugar of Patient 2 rose from 0.068 to 0.094 per cent. The patient then moved to a distant city and the course of the disease could not be followed.

ACIDOSIS

On account of the relationship of changes in the acid-base equilibrium to disturbances of the metabolism of sugar and creatin, the ammonia excretion in the urine was determined from day to day; but in none of our cases did it ever rise higher than 0.43 gm. per day — a figure that is well within the normal limits.

SUMMARY

In three cases of progressive muscular dystrophy were found: (1) muscular weakness, (2) hypoglycemia, (3) hypocholesterinemia, (4) creatinuria, (5) normal ammonia excretion, (6) a rise of blood sugar in the treated patients with a parallel increase in strength.

A comparison of the findings in three somewhat similar clinical conditions showed the following:

	Blood Sugar	Creatinuria
Progressive muscular dystrophy....	Low	Present
Progressive muscular atrophy.....	Normal	Present
Myasthenia gravis.....	Low	Absent

REFERENCES

1. McCrudden, F., and Sargent, C.: Hypoglycemia and Progressive Muscular Dystrophy, THE ARCHIVES INT. MED., 1916, **17,** 465.

2. The technical details of the methods are described in our previous paper.

3. Since Dr. George Clymer, neurologist to the Robert B. Brigham Hospital, who searched the community and found these myasthenic cases, is now in the national service abroad, we see no probability of obtaining any more cases in the near future.

6. Blood sugar appears to remain fairly constant from day to day in any one individual: (32) January 3: 0.145 per cent.; July 5: 0.147 per cent.; (33) August 20: 0.159 per cent.; August 23: 0.159 per cent.; (42) December 17: 0.095 per cent.; December 30: 0.092 per cent.

7. It is to be regretted that the very useful normal figures recently reported by Gettler and Baker (Jour. Biol. Chem., 1916, **25,** 211) were not controlled by duplicate analyses. Some of the extreme figures would then be less open to suspicion.

8. On a meat-free diet.

THE NATURE OF THE PATHOLOGIC PROCESS IN PROGRESSIVE MUSCULAR DYSTROPHY

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In progressive muscular dystrophy we find: (*a*) low blood sugar, and, following suitable treatment, a rise in blood sugar accompanied by an increase in strength; (*b*) creatinuria; (*c*) low cholesterin content of the blood — three independent testimonies of disturbed carbohydrate metabolism.[1]

The condition of low blood sugar and parallelism between muscular strength and blood sugar speaks for itself.

Creatin is not known to occur in the urine of men except as an accompaniment of some disturbance of carbohydrate metabolism. It accompanies diabetes and starvation. In dogs it accompanies hydrazin poisoning,[2] and phlorizin poisoning,[3] conditions resulting in hypoglycemia.[4] In the rabbit, an animal in which hypoglycemia does not always follow hydrazin poisoning, creatinuria occurs only in those cases in which hypoglycemia does follow.[5]

A low cholesterin content of the blood accompanies hypoglycemia;[1] a high cholesterin content is associated with hyperglycemia.[6]

The glucose of the blood is the source of energy for muscular contraction. Active muscle rapidly uses up glucose. It may use more than six times as much as the resting muscle;[7] the venous blood from a faradized muscle may show only one half as much glucose as that from a resting muscle.[8] Following severe muscular activity the blood sugar, even of the general circulation, may fall;[9] during the severe convulsions of tetanus it may fall to one third the normal.[10] As the blood sugar falls, muscular power diminishes, but can be restored by glucose.[11]

The dynamic potency of glucose has been especially clearly demonstrated for heart muscle. The isolated heart perfused with Ringer's solution beats more and more feebly as its glycogen store becomes exhausted, and finally stops. If glucose is added to the perfusion fluid this sugar is utilized[12] and the heart beats more powerfully and for a longer time.[13] The utilization of glucose by muscle is a complicated physiologic process; it is lost if removal of the pancreas precedes isolation of the heart,[14] but can be restored by addition of pancreas extract to the perfusion fluid.[14] The property is inherent in glucose alone; other sugars are impotent.[15]

Besides muscular activity, certain other agencies may reduce the blood sugar — Addison's disease,[16] adrenalectomy,[17] dyspituitarism,[18] thyroidectomy and parathyroidectomy,[19] diphtheria toxin,[20] phosphorus poisoning,[21] and hydrazin poisoning,[4] and such agencies all produce profound asthenia. In phosphorus poisoning and diphtheria toxemia the parallelism between severity of myasthenia and decrease in blood sugar is very marked;[22] and in successfully treated Addison's disease a parallelism between increase in strength and rise in blood sugar has been observed (Grote[10]).

It is evident that the low blood sugar in progressive muscular dystrophy is a sufficient cause for the muscular weakness, the most striking symptom of the disease.

As glucose passes from the blood into the tissues, the loss is made good from the glycogen store of the liver. Replenishment is rapid and quantitative, the blood sugar being thereby maintained at a fixed level. Hypoglycemia can result only from a failure of replenishment to keep pace with the needs, a loss of balance between supply and demand.

Increased needs might result from increased sugar utilization or from loss through the kidneys. We can rule out both. There is neither the rise in temperature nor the increase in rate of heat loss that would accompany increased sugar catabolism; and the urine is sugar-free.[1]

The cause of all forms of experimental hypoglycemia is a decreased rate of replenishment consequent on a diminished glycogen reserve. After thyreoparathyroidectomy,[23] adrenalectomy,[24] diphtheria toxemia,[20] phosphorus poisoning,[25] hydrazin poisoning,[26] the liver and muscles contain far less than the normal quantity of glycogen, in some cases little or none.

In progressive muscular dystrophy a rapid fall of blood sugar during the first twenty-four hours of starvation testifies to a scanty glycogen store in this condition too; in health the normal blood sugar level is tenaciously maintained throughout prolonged starvation.[27]

The diminished glycogen reserve in experimental hypoglycemia results from impaired glycogenesis. The carbohydrate ingested is not converted into glycogen (Porges[25]). The liver of the adrenalectomized animal, for example, does not store any glycogen even when glucose enough is ingested to increase the blood sugar fivefold (Mackenzie[24]). The glucose remains a long time in the blood;[28] and then, judging from the amount of "fatty degeneration" in these cases — adrenalectomy,[29] phosphorus poisoning,[21] hydrazin poisoning,[30] dyspituitarism[18] — it is probably changed to fat. The rise in the respiratory quotient[31] and the increase in the fat content of the blood[32] lend further support to this hypothesis. Such antagonism between fat storage and glycogen storage is well recognized.[33]

The deposition of fat in the muscles[34] in progressive muscular dystrophy is evidence in this condition of a similar impairment of glycogenesis.

Impaired glycogenesis may result from either liver or adrenal damage. After phosphorus or hydrazin the result is due to liver destruction; after adrenalectomy or Addison's disease, to absence of epinephrin. It is possible to tell which of the two—liver or adrenal—is at fault by the effect of epinephrin administration. Normally, epinephrin[35] administration decreases the glycogen of the liver,[36] and thereby increases the glucose of the blood;[37] but it does not increase the blood sugar to the same extent after liver damage.[38] During the first twenty-four hours after phosphorus poisoning while the liver is still intact, epinephrin increases the blood sugar; after the first twenty-four hours, liver injury precludes epinephrin activity.[21]

The prompt and marked rise in blood sugar following epinephrin administration in progressive muscular dystrophy testifies to the adrenal rather than the hepatic origin of the disease.[1]

The possibility that alkalosis plays a part in the etiology of progressive muscular dystrophy was suggested by the following facts connecting alkalosis, hypoglycemia and creatinuria:

(*A*). *Alkalosis and Hypoglycemia.* — (*a*) Alkali administration causes hypoglycemia;[39] it diminishes, and may even prevent epinephrin hyperglycemia and glycosuria.[40] (*b*) Acid administration increases glycogenolysis, causes hyperglycemia, and augments epinephrin hyperglycemia (Elias[39]). (*c*) If a frog be kept in a slightly acid solution its store of glycogen diminishes; if in an alkaline solution, the glycogen store augments.[41] (*d*) A base forming diet is more efficient as a glycogen former,[42] and gives a greater epinephrin glycosuria[43] than an acid forming diet. (*e*) Epinephrin hyperglycemia is accompanied by a decrease,[44] and thyreoparathyroidectomy by an increase, in the alkali reserve of the blood.[45]

(*B*). *Alkalosis and Creatinuria.*—(*a*) In rabbits creatinuria follows administration of acid or an acid diet,[46] in which case the urine is always acid.[47] (*b*) Alkali administration diminishes, and sometimes abolishes, the creatinuria of starvation.[48]

But alteration in the acid-base equilibrium severe enough to produce hypoglycemia leads to marked changes in the reaction of the urine,[49] and such changes are not present in progressive muscular dystrophy — ammonia excretion is normal. This is in harmony with the other evidence that the hypoglycemia of progressive muscular dystrophy is of endocrine origin. The adrenals are not involved in the blood sugar variations brought about by changes in the acid-base equilibrium (Elias[39]).

Another possibility: It is alleged[50] that epinephrin decreases, and that the internal secretion of the pancreas increases the rate of sugar oxidation; and that normally the two tendencies — inhibiting and stimulating — just balance. In accord with this hypothesis, epinephrin hyperglycemia is attributed to loss of balance in favor of — diminished glucose destruction — the suprarenal; and progressive muscular dystrophy might be attributed to corresponding loss of balance in favor of — increased sugar oxidation — the pancreas. But epinephrin does not decrease the rate of glucose destruction,[51] and all the evidence points to diminished glucose formation and not augmented glucose destruction as the cause of the hypoglycemia in progressive muscular dystrophy.

The facts indicate that the myasthenia of progressive muscular dystrophy is due to hypoglycemia; that the hypoglycemia and fatty infiltration are due to impaired glycogenesis, the carbohydrate of the food being probably changed largely to fat instead of glycogen; and that this impaired glycogenesis is the result of adrenal or other endocrine disease.

BIBLIOGRAPHY

1. McCrudden, F. H., and Sargent, C.: Hypoglycemia and Progressive Muscular Dystrophy, THE ARCHIVES INT. MED., 1916, **17,** 465. Ibid., Chemical Changes in the Blood and Urine in Progressive Muscular Dystrophy, Progressive Muscular Atrophy, and Myasthenia Gravis, THE ARCHIVES INT. MED., this issue, p. 252.

2. Underhill, F., and Kleiner, I.: The Influence of Hydrazin Poisoning on Intermediary Metabolism in the Dog, Jour. Biol. Chem., 1908, **4,** 165.

3. Underhill, F., and Baumann, E.: Studies in Creatin Metabolism. III. The Influence of Alkali on the Creatinuria of Phlorhizin Glycosuria, Jour. Biol. Chem., 1916, **27,** 147.

4. Underhill, F.: Studies in Blood Sugar Metabolism. I. The Influence of Hydrazin on the Organism, with Special Reference to the Blood Sugar Content, Jour. Biol. Chem., 1911, **10,** 159.

5. Macadam: The Relationship of Creatinuria to Changes in the Sugar Content of the Blood, Biochem. Jour., 1915, **9,** 229.

6. Fischer, B.: Ueber Lipämie und Cholesterämie, sowie über Veränderungen des Pankreas und der Leber bei Diabetes Mellitus, Arch. f. path. Anat., 1903, **172,** 30. Bloor, W.: The Lipoids ("Fat") of the Blood in Diabetes, Jour. Biol. Chem., 1916, **26,** 417. Joslin, E., Bloor, W., and Gray, H.: The Blood Lipoids in Diabetes, Jour. Am. Med. Assn., 1917, **69,** 375.

7. Morat and Dufourt: Consommation du sucre par les muscles, Arch. de physiol., 1892, **24,** 327.

8. Quinquaud, C.: Expériénce sur la contraction musculaire et la chaleur animale, Compt. rend. Soc. de biol., 1886, **38,** 410.

9. Chauveau, M., and Kaufmann, M.: Expériénce pour la détermination du coefficient de l'activité nutritive et respirative des muscles en repos et en travail, Compt. rend. Acad. d. sc., 1887, **104,** 1126. Ibid., Consequences physiologiques de la détermination de l'activité specifique des échanges ou du coefficient de l'activité nutritive et respirative dans les muscles en repos et en travail, Compt. rend. Acad. d. sc., 1887, **104,** 1352 and 1763. Weiland, W.: Ueber den Einfluss ermüdender Muskelarbeit auf den Blutzuckergehalt, Arch. f. klin. Med., 1908, **92,** 223.

10. The hypoglycemia accompanying thyreoparathyroidectomy has a different cause; it precedes the tetany, and cannot, therefore, be the result of the tetany. Underhill, F., and Blatherwick, N.: Studies in Carbohydrate Metabolism. VII. The Influence of Subcutaneous Injections of Dextrose and of Calcium Lactate on the Blood Sugar Content and on Tetany after Thyreoparathyroidectomy, Jour. Biol. Chem., 1914, **19,** 119. Refer also to Grote, L.: Blutzucker und Diättherapie bei morbus Addisoni, München. med. Wchnschr., 1916, **63,** 1614. Pnrjesz, B.: Der Blutzuckergehalt unter normalen und pathologischen Verhältnisse, Wien. klin. Wchnschr., 1913, **26,** 1420.

11. Furth and Schwarz: Ueber die Steigerung des Warmblütermuskels durch gerinnungsbefördende Muskelgift, Pflüger's Arch. f. d. ges. Physiol., 1909, **129,** 525.

12. Locke, F., and Rosenheim, O.: The Disappearance of Dextrose Through the Isolated Mammalian Heart, Proc. Physiol. Soc., March 19, 1904, Jour. Physiol., 1904, **31,** 14; Ibid., Contributions to the Physiology of the Isolated Heart, Jour. Physiol., 1907-1908, **36,** 205.

13. Locke, F.: Toward the Ideal Artificial Circulating Fluid for the Isolated Frog's Heart, Jour. Physiol., 1895, **18,** 332; Ibid., Die Wirkung der Metalle des Blutplasmas und verschiedener Zucker auf das isolirte Säugethierherz, Centralbl. f. Physiol., 1901, **14,** 670; Ibid., The Action of Dextrose on the Isolated Mammalian Heart, Proc. Physiol. Soc., March 19, 1904, Jour. Physiol., 1904, **31,** 13.

14. Knowlton, F., and Starling, E.: Experiments of the Consumption of Sugar in the Normal and the Diabetic Heart, Jour. Physiol., 1912-1913, **47,** 147.

15. Locke, F., and Rosenheim, O.: The Effect of Certain Sugars on the Isolated Mammalian Heart, Proc. Physiol. Soc., March 19, 1904, Jour. Physiol., 1904, **31,** 14.

16. Refer to Footnote 10. Porges: Ueber Hypoglykämie bei Morbus Addison sowie bein ebennierlosen Hunden, Ztschr. f. klin. Med., 1909-1910, **69,** 341. Bernstein, S.: Ueber den Blutzuckergehalt bei Addison'scher Krankheit, Berl. klin. Wchnschr., 1911, **48,** 1794. Schirokauer, H.: Zum Zuckerstoffwechsel bei Addison'scher Krankheit, Berl. klin. Wchnschr., 1911, **48,** 1505. Rolly, F., and Opperman, F.: Das Verhalten des Blutzucker bei Gesunden und Kranken. VI. Mitteilung. Der Blutzuckergehalt bei Anämie, Leber, Darm und anderen Erkrankungen des Menschen, Biochem. Ztschr., 1913, **48,** 471.

17. Refer to Porges, Footnote 16. Bierry, H., and Malloizel, L.: Hypoglycémia après décapsulation. Effects de l'injection d'adrénaline sur les animaux décapsulés, Compt. rend Soc. de biol., 1908, **65,** 232. Mayer: Ablation des surrénales et diabéte pancréatique, Compt. rend. Soc. de biol., 1908, **64,** 219.

18. Cushing, H.: The Pituitary Body and Its Disorders, Phila., 1910, p. 130.

19. Janney, N., and Isaacson, V.: The Influence of Thyroidectomy on the Blood Sugar, Proc. Soc. for Exper. Biol. and Med., 1907, **14,** 99.

20. Rosenthal, F.: Störungen des Kohlenhydratstoffwechsels bei der experimentellen Diphtherievergiftungen, Arch. f. exper. Path. u. Pharmakol., 1913-1914, **75,** 99.

21. Frank, E., and Isaac, S.: Ueber das Wesen des zerstörten Stoffwechsels bei der Phosphovergiftung, Arch. f. exper. Path. u. Pharmakol., 1910-1911, **64,** 274.

22. Refer to Footnotes 20 and 21.

23. Underhill, F., and Blatherwick, A.: Studies in Carbohydrate Metabolism. VI. The Influence of Thyreoparathyroidectomy on the Sugar Content of the Blood, Jour. Biol. Chem., 1914, **18,** 87.

24. Refer to Porges, Footnote 16, and the following: Schwartz: Ber. der Gesellsch. der Arzte in Wien. Wien. klin. Wchnschr., 1909, **59,** 3016. Schwarz, O.: Ueber Stoffwechselstörungen nach der Extirpation der Nebennieren, Pflüger's Arch. f. d. ges. Physiol., 1910, **134,** 259. Kahn, R., and Starkenstein, E.: Ueber das Verhalten des Glykogens nach Nebennierenextirpation, ibid., 1911, **139,** 181. Mackenzie: Suprarenal System and Carbohydrate Metabolism, THE ARCHIVES INT. MED., 1917, **19,** 593.

25. Porges: Zur Pathologie des Morbus Addison. II. Ueber Glykogenschwund nach doppelseitiger Nebennierenextirpation bei Hunden, Ztschr. f. klin. Med., 1910, **70,** 243. Refer also to Frank and Isaac, Footnote 21.

26. Underhill, F.: Refer to Footnote 4, and Studies in Carbohydrate Metabolism. III. The Influence of Hydrazine on Glycogen Storage in the Organism (and on Blood Composition), Jour. Biol. Chem., 1914, **17,** 293.

27. Allen, F.: Glycosuria and Diabetes, 1913.

28. Underhill, F., and Hogan, A.: Studies in Carbohydrate Metabolism. VIII. The Influence of Hydrazine on the Utilization of Dextrose, Jour. Biol. Chem., 1915, **20,** 203. Refer also to Footnotes 19, 20 and 21.

29. Porges: Zur Pathologie des Morbus Addison. II. Ueber Glykogenschwund nach doppelseitiger Nebennierenextirpation bei Hunden, Ztschr. f. klin. Med., 1910, **70,** 243.

30. Wells, H.: The Pathological Anatomy of Hydrazine Poisoning, Jour. Exper. Med., 1908, **10,** 457.

31. Underhill, F., and Murlin, J.: Studies in Carbohydrate Metabolism. X. The Influence of Hydrazin on the Respiratory Quotient and on Heat Production, Jour. Biol. Chem., 1915, **22,** 499.

32. Underhill, F., and Baumann, E.: The Interrelation of Blood Fat and Blood Sugar Content of Dogs Under the Influence of Hydrazine, Jour. Biol. Chem., 1916, **27,** 169.

33. Rosenfeld: Fettbilding, Ergebn. d. Physiol., 1902, **1,** 651.

34. So marked in some cases that the term "pseudohypertrophic" is applied. We might hazard the conjecture that some cases of myocarditis with fatty infiltration are pseudohypertrophic muscular dystrophy of the heart, and that they might be helped by epinephrin. In one such case we found only 0.0662 per cent. glucose in the blood. The "fatty degeneration" of the heart occurring in diphtheria and certain other infectious diseases may be similar in nature.

35. And certain other endocrine principles.

36. Doyon, M., and Kareff, N.: Action de l'adrénaline sur le glycogène du foie, Compt. rend Soc. de biol., 1904, **56,** 66. Agadschanianz, K.: Ueber den Einfluss des Adrenalines auf das in Leber und Muskeln enthaltende Glykogen, Biochem. Ztschr., 1906, **2,** 148. Gatin-Gruzewska, Z.: Action de l'adrénaline sur la teneur du muscle en glycogène, Compt rend. Acad. d. sc., 1906, **142,** 1165.

37. The first papers on this subject were: Blum, F.: Ueber Nebennierendiabetes, Deutsch. Arch. f. klin. Med., 1901, **71,** 146; Blum, F.: Weitere Mittheilungen zur Lehre von dem Nebennierendiabetes, Pflüger's Arch. f. d. ges. Physiol., 1902, **90,** 617; Zuelzer, G.: Zur Frage des Nebennierendiabetes, 1901, **38,** 1209.

It stimulates the reverse process when food is ingested (Footnotes 25 and 38).

38. Pollack, L.: Experimentelle Studien über Adrenalin-Diabetes, Arch. f. exper. Path. u. Pharmakol., 1909, **61,** 153. Ringer, A.: The Influence of Adrenalin in Phlorhizin Diabetes, Jour. Exper. Med., 1910, **12,** 105. Herter, C., and Richards, A.: Note on the Glycosuria Following Experimental Injection of Adrenalin, Medical News, 1902, **80,** 201. Frank, E., and Isaac, S.: Die Bedeutung des Adrenalins und des Cholin für die Erforschung des Zuckerstoffwechsels, Ztschr. f. exper. Path. u. Therap., 1910, **7,** 326. Velicke, A.: Beitrag zum Experimentalstudium von Nebennieren-Glykosurie, Virchow's Arch. f. path. Anat., 1906, **184,** 345. Falta, W., and Priestly, G.: Beiträge zur Regulation von Blutdruck und Kohlenhydrat-Stoffwechsel durch das Chromaffine-System, Berl. klin. Wchnschr., 1911, **48,** 2102. Michaud: Ueber den Kohlenhydratstoffwechsel bei Hunden mit Eckschen Fistel, Verhandl. d. Deutsch. Cong. f. inn. Med., Wiesbaden, 1911, **28,** 561.

39. Underhill, F.: Studies in Carbohydrate Metabolism. XII. The Influence of Sodium Carbonate on Blood Sugar Content and on Epinephrin Hyperglycemia, Jour. Biol. Chem., 1916, **25,** 463. Elias: Ueber die Rolle der Säure im Kohlenhydratstoffwechsel. Ueber Säurediabetes, Biochem. Ztschr., 1913, **48,** 120.

40. McDanell, L., and Underhill, F.: Studies in Carbohydrate Metabolism. XVII. Further Experiments on the Influence of the Intravenous Injection of Sodium Carbonate on the Epinephrin Hyperglycemia and Glycosuria, Jour. Biol. Chem., 1917, **29,** 251. Refer also to Footnote 39.

41. Ehrlich, P.: Das Leberglykogen des Frosches betreffendes Schreiben an den Herausgeber, Pflüger's Arch. f. d. ges. Physiol., 1907-1908, **121,** 236.

42. McDanell, L., and Underhill, F.: Studies in Carbohydrate Metabolism. XVIII. The Relation of Diet to the Glycogen Content of the Liver, Jour. Biol. Chem., 1917, **29,** 255.

43. McDanell, L., and Underhill, F.: Studies in Carbohydrate Metabolism. XVI. The Relation of Epinephrin Glycosuria to Dosage and to the Character of the Diet, Jour. Biol. Chem., 1917, **29,** 245.

44. Peters, J., and Geyelin, H.: The Relation of Adrenalin Hyperglycemia to Decreased Alkali Reserve of the Blood, Jour. Biol. Chem., 1917, **31,** 471.

45. Wilson, D., Stearns, T., and Thurlow, M.: The Acid-Base Equilibra in the Blood after Parathyroidectomy, Jour. Biol. Chem., 1915, **23,** 89. Wilson, D., Stearns, F., and Janney, J.: The Excretion of Acids and Ammonia after Parathyroidectomy, Jour. Biol. Chem., 1915, **23,** 123.

46. Underhill, F.: Studies in Creatine Metabolism. I. Possible Interrelation Between Acidosis and Creatin Elimination, Jour. Biol. Chem., 1916, **27,** 127.

47. Underhill, F., and Bogert, L.: Alteration in the Output of Certain Urinary Constituents as Determining Changes in the Character of the Diet, Jour. Biol. Chem., 1916, **27,** 161.

48. Underhill, F.: Studies in Creatin Metabolism. II. The Influence of Alkali on Creatin Elimination During Inanition, Jour. Biol. Chem., 1916, **27,** 141.

49. McDanell, L., and Uunderhill, F.: Studies in Carbohydrate Metabolism. XV. The Influence of Acid-Forming and of Base-Forming Diets on Blood Sugar Content, Jour. Biol. Chem., 1917, **29,** 233.

50. Eppinger, H., Falta, W., and Rudinger, C.: Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion, Ztschr. f. klin. Med., 1908, **66,** 1.

51. Lusk, G.: Animal Calorimetry. Paper VIII. The Alleged Influence of the Adrenals on Diabetic Metabolism, The Archives Int. Med., 1914, **13,** 673.

THE EFFECT OF THYROID SECRETION ON THE EXCITABILITY OF THE ENDINGS OF THE CARDIAC VAGUS *

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In an earlier communication[1] it was pointed out that, in the cat, after inducing secretory activity in the thyroid gland, either by stimulation of the cervical sympathetic nerves or by injection of small doses of epinephrin, there can be demonstrated an increased effectiveness of epinephin as a pressor agent. In other words, thyroid secretion renders more excitable those sympathetic structures acted on by epinephrin in raising arterial pressure. It was further shown that this effect is manifest only after a latent period, which may vary from about forty to sixty minutes, and that it is of considerable duration, having been observed for as long as seven hours.

A number of investigators, notably Asher and von Rodt,[2] Ossokin[3] and Oswald[4] maintain that thyroid secretion increases the responsiveness of vagus terminations to electrical stimulation. If this be true, thyroid secretion must be regarded as having a sensitizing effect on both true sympathetic as well as on parasympathetic (vagus) endings. Their work, however, is open to three serious criticisms. In the first place, all employed intact animals under anesthesia; under such conditions, owing to variations in the depth of anesthesia as well as to respiratory and vasomotor fluctuations, it is practically impossible to obtain uniform vagus responses to a given strength of stimulus. Secondly, in some of the experiments (Asher and von Rodt[2] and Ossokin[3]), thyroid secretion is said to have been poured into the circulation as a result of stimulation of the laryngeal nerves; these nerves, according to recent work,[5] are in no way directly concerned with secretory discharge in the thyroid gland. And finally, Oswald's results were obtained after injection of iodthyreoglobulin, a preparation which this author assumes is the active principle of the thyroid. The variability and unreliability of effects which may be observed by employing dif-

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* From the Medical Clinic of the Johns Hopkins Hospital.

1. Levy, R. L.: Am. Jour. Physiol., 1916, **41,** 492.
2. Asher, L., and von Rodt, W. E.: Zentralbl. f. Physiol., 1912, **26,** 223.
3. Ossokin, N.: Ztschr. f. Biol., 1914, **63,** 443.
4. Oswald, A.: Zentralbl. f. Physiol., 1915, **30,** 509; also Arch. f. ges. Physiol., 1916, **164,** 506.
5. Cannon, W. B., and Cattell, McK.: Am. Jour. Physiol., 1916, **41,** 58.

ferently prepared glandular extracts are too well known to require comment.

It was the object of the present investigation to determine the effect of thyroid secretion on the excitability of the endings of the cardiac vagus under conditions which would meet satisfactorily the foregoing criticisms.

METHODS

The methods employed were, in their essentials, similar to those used in the writer's previous work.[1]

Cats were used in all the experiments. During preliminary ether anesthesia, a tracheal cannula was inserted and to destroy the brain a perforation was made in the back of the orbit and a probe passed through it into the spinal canal beyond the level of the medulla. Artificial respiration, carefully adjusted as to depth and rate and maintained by a motor-driven, air-blast interrupter, was now begun. The cervical sympathetic nerves were dissected free from the vagus sheaths for 3 or 4 cm., ligated low in the neck and severed distal to the ligatures. The depressor, when present as a separate nerve, was also cut. The vagi were likewise isolated, ligated high in the neck and cut above the ligatures. The probe was now again inserted through the orbit and the cord thoroughly destroyed to about the level of the second or third thoracic segment. Usually, in the course of twenty minutes or half an hour, the blood pressure fell to a constant level at about 50 mm. Hg. An electric heating pad placed beneath the animal holder permitted the maintenance of a normal, or nearly normal, temperature.

In cats pithed in this manner, the resulting rise in blood pressure after an injection of epinephrin varies directly with the amount injected. Vasomotor and respiratory fluctuations are abolished. The circulatory system responds with almost mathematical precision to repeated injections of a given dose.

It was also found that, in these animals, repeated stimulation of the vagus with a given strength of stimulus results in uniform cardiac responses. Both depth of depression of blood pressure and duration of inhibition are so constant that, over a period of hours, each of the series of curves can practically be superimposed on the preceding ones. The result is the same whether right or left vagus is stimulated. The pithed cat is, therefore, an excellent preparation for determining alterations in excitability of the cardiac vagus.

A Sherrington electrode[6] was placed on one vagus and connected, through a signal magnet, with a tetanizing circuit. The strength of stimulus employed approached as nearly as possible the threshold of excitability, which was determined at the beginning of each experiment.[7] Less uniform, though comparable, results were obtained by employing an ordinary platinum stimulating electrode, the vagi being carefully moistened and protected between stimulations.

A cannula inserted into the femoral artery was connected with a mercury manometer, sodium carbonate being used as anticoagulant. Injections of epinephrin were made through another cannula placed in the femoral vein on the opposite side. A slowly revolving kymograph was used to record the effects of epinephrin injections, a more rapidly moving one for the vagus responses.

The epinephrin employed was the commercial "Adrenalin Chloride" of Parke, Davis & Co., and was fresh. Immediately before each experiment it was diluted, 1:100,000, with distilled water. The injections were made from a syringe

6. Sherrington, C. S.: Jour. Physiol., 1909, **38**, 375.

7. The pithed cat is such a delicate preparation that a measurably effective vagal stimulus frequently causes complete cardiac inhibition. In experiments in which only slowing of rate occurred, the results were the same as where complete inhibition followed stimulation.

with 1 c.c. barrel, graduated to fiftieths of a cubic centimeter. A metronome, beating at intervals of one second, permitted delivery of the dose uniformly in successive injections. Usually 0.2 c.c. were injected at the rate of 0.02 c.c. per second.

For stimulating the cervical sympathetic nerves, a tetanizing current, rhythmically interrupted at the rate of about 25 or 30 times a minute, was employed, the nerve being laid over a platinum electrode. The current was of such strength that it could comfortably be borne on the tip of the tongue and always caused maximal pupillary dilatation when the side with intact eye was stimulated.

A time marker registering 30-second intervals during the epinephrin injections and 5-second intervals when vagus stimulations were recorded on the more rapidly revolving drum, served also as base line for zero blood pressure level.

RESULTS

In cats prepared as described, repeated stimulation of either vagus over a period of several hours gives a uniform series of responses. It is possible to obtain practically an identical curve with a given strength of stimulus from either right or left vagus. At least five minutes were permitted to elapse between successive stimulations, in order that the heart might fully recover its irritability.

After stimulation of the cervical sympathetic, even at a time when increased pressor response to a given dose of epinephrin gives evidence that there has been liberation of thyroid secretion, there is no significant alteration in depressor effect or duration of inhibition following stimulation of either vagus nerve. It is therefore evident that, after the thyroid gland has poured forth its secretion in sufficient amount to sensitize the sympathetic structures acted on by epinephrin in raising arterial pressure, there is no demonstrable effect on the excitability of the endings of the cardiac vagus. In the illustration are pictured the records of such an experiment, and in the table is given the complete protocol, which serves as an illustration for the series.

Similarly, uniform vagus responses were obtained when, instead of stimulating the cervical sympathetic, a small dose of epinephrin (2 c.c. of 1 : 100,000) was injected to induce secretory activity in the thyroid.

It has been shown repeatedly[8] that an injection of epinephrin causes a temporary decrease in the irritability of the cardiac vagus, this effect in the cat, according to Langley, lasting only from one to two minutes. The epinephrin injections in no way modified the effects of vagus stimulation in the present series of experiments. An interval of at least eight minutes was permitted to elapse between any vagus stimulation and the preceding epinephrin injection. To bring final proof, a number of experiments were performed in which, after taking the

8. Cybulski, N.: Anzeiger d. Akad. d. Wissensch. in Krakau, March 4, 1895. Gourfein, D.: Compt. rend. Acad. d. sc., 1895, **121,** 311. Langley, J. N.: Jour. Physiol., 1901, **27,** 245. Barbour, H. G., and Kleiner, S. B.: Jour. Pharmacol. and Exp. Therap., 1915, **7,** 541.

usual vagus controls, each cervical sympathetic was stimluated for five minutes. No epinephrin was injected, yet, though presumably the thyroid glands had been vigorously stimulated, no alteration in the character of the vagus responses was observed over a period of several hours.

Illustrative Protocol. (The records of this experiment, except Epinephrin Injection 6, are reproduced in the accompanying illustration.)

Male cat; weight, 2.6 kg.

9:20. Ether.

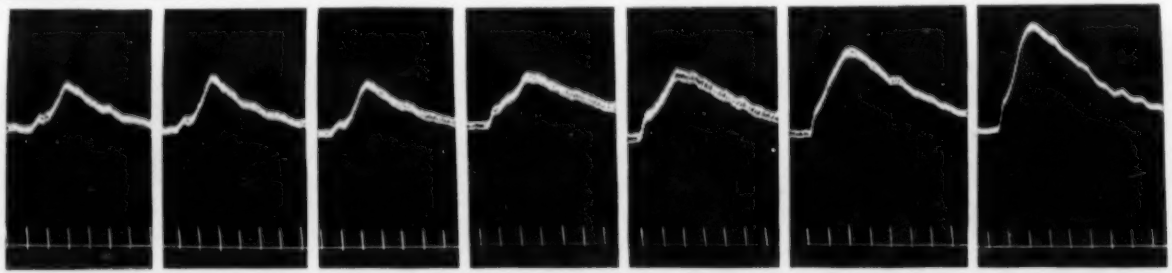
9:25-9:45. Tracheotomy. Pithed to midthorax; artificial respiration begun; vagi and sympathetics dissected out, ligated and cut; Sherrington electrode placed on right vagus; each epinephrin injection 0.2 c.c., 1:100,000, injected at the rate of 0.02 c.c. per second. The duration of each vagus stimulation was three seconds.

Time	Procedure	Rise in Blood Pressure Following Epinephrin Injection (Mm. Hg.)	Effects of Vagus Stimulation	
			Depression of Blood Pressure (Mm. Hg.)	Duration of Cardiac Inhibition (Seconds)
10:25	Epinephrin injection 1	19		
10:31	Epinephrin injection 2	22		
10:40	Stimulation of right vagus	..	19	3.7
10:47	Stimulation of right vagus	..	19	3.4
10:51-10:57	Stimulation of left cervical sympathetic			
11:02	Epinephrin injection 3	22		
11:15	Stimulation of right vagus	..	19	3.7
11:50	Epinephrin injection 4	23		
12:00	Stimulation of right vagus	..	18	3.5
12:10	Epinephrin injection 5	29		
12:30	Epinephrin injection 6	34		
12:45	Epinephrin injection 7	38		
1:00	Stimulation of right vagus	..	17	3.7
1:15	Epinephrin injection 8	48		
1:22	Stimulation of right vagus	..	18	3.8
1:28	Stimulation of left vagus	..	18	3.9

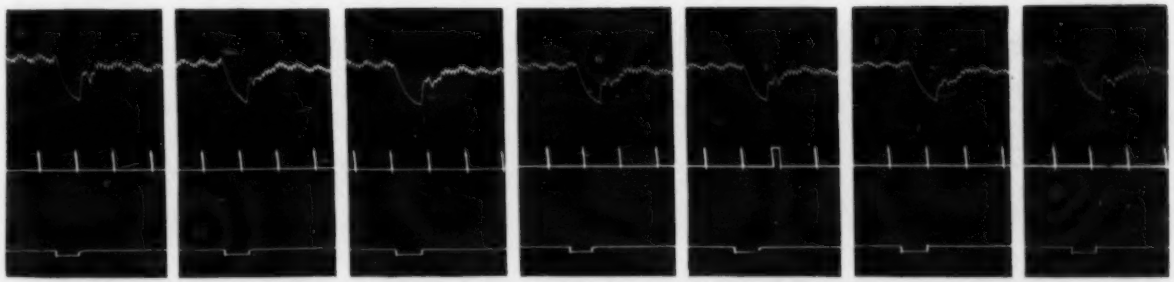
SUMMARY

1. In cats pithed to midthorax, repeated stimulation of either vagus with a given strength of stimulus results in a uniform series of responses, both as to degree of depressor effect and duration of cardiac inhibition. The pithed cat is, therefore, an excellent preparation for determining alterations in the excitability of the cardiac vagus.

2. After inducing secretory activity in the thyroid gland, even at a



1A 2A 3A 4A 5A 6A 7A



1B 2B 3B 4B 5B 6B 7B

(The protocol of this experiment is given in the accompanying table.)

The curves in the upper row (A) show rises in blood pressure after injection of 0.2 c.c. of epinephrin, 1:100,000. The time marker records 30-second intervals and is at zero blood pressure level.

The lower tracings (B) show the effects of vagus stimulation. The time marker records 5-second intervals and is at zero blood pressure level. A signal magnet marks on the lowest line the three seconds during which the stimulus was maintained.

1 A and 2 A, controls, taken 6 minutes apart. (20 minutes after 2 A, the left cervical sympathetic was stimulated for 6 minutes.) 3 A, 5 minutes after stimulation. 4 A, 53 minutes after stimulation. 5 A, 73 minutes after stimulation. 6 A, 108 minutes after stimulation. 7 A, 138 minutes after stimulation.

1 B and 2 B, controls, taken 7 minutes apart. (4 minutes after 2 B, the left cervical sympathetic was stimulated for 6 minutes.) 3 B, 18 minutes after stimulation. 4 B, 63 minutes after stimulation. 5 B, 123 minutes after stimulation. 6 B, 146 minutes after stimulation. 7 B, 151 minutes after stimulation.

time when increased pressor response to a given dose of epinephrin gives evidence that there has been a pouring out of thyroid secretion, there is no significant alteration in depressor effect or duration of cardiac inhibition following stimulation of either vagus nerve.

3. It is therefore evident that after the thyroid gland has liberated its secretion in sufficient amount to sensitize the sympathetic structures acted on by epinephrin in raising arterial pressure, there is no demonstrable effect on the excitability of the endings of the cardiac vagus.

THE MAINTENANCE DIET IN DIABETES MELLITUS AS DETERMINED BY THE NITROGEN EQUILIBRIUM *

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AND
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In the treatment of diabetes mellitus there are two guiding principles which determine the caloric value of the diet. In the first place, the quantity of carbohydrates, proteins and fats offered the patient must be within his carbohydrate tolerance; that is, the diet must be so regulated that the urine remains sugar-free. It is generally acknowledged that under these circumstances the disease itself is treated in the most effective manner. Secondly, a diet of sufficient caloric value should be offered the patient so that his health and strength may be maintained at a normal level. It is readily appreciated that these two guiding principles of treatment are diametrically opposed to each other in many respects. The one demands a restricted diet, and in many instances, undernutrition; the other calls for a larger amount of food. The first aims at treating the disease, diabetes mellitus; the second attempts to conserve the nutrition of the patient. The neglect of either factor may entail undesirable results.

During the past years emphasis has been continually placed on the dietary restriction and the prevention of glycosuria. Previously, on account of lack of full appreciation of the results which could be obtained by a more drastic curtailment of the food calories, this idea was not pushed to its logical conclusion of controlling the glycosuria of nearly every diabetic patient. Through the efforts of F. M. Allen, by systematic and radical reductions in the food, this may be easily accomplished in most cases.[1] The widespread use of these very limited diets has brought up the question of how little the individual may eat and yet remain physically and mentally fit. It is the object of the present paper to furnish at least a partial answer to this question.

At present it is believed that "diabetics generally have no higher food requirement than normal, and, on account of undernutrition and lessened muscular activity, will tend to maintain equilibrium on a smaller number of utilizable calories than normal persons."[2] One factor which the above statement implies is that the lower the nutri-

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1. Allen, F. M.: Boston Med. and Surg. Jour., 1915, **172**, 241.
2. Allen, F. M., and Du Bois, E. F.: THE ARCHIVES INT. MED., 1916, **17**, 1010.

tional state of a diabetic or anyone else becomes, the less will be the food requirements necessary to reach a maintenance level. When such a subnormal state is reached, and the main object of treatment is to keep the patient alive and not necessarily efficient, a partial failure in our therapeutic aims must be acknowledged. The maintenance diet, under ideal conditions, should be sufficiently high not only to enable the patient to live, but also to carry on an average amount of physical and mental work without undue fatigue.

The standard for maintenance for the diabetic may be sought for in one of two criteria: first, the caloric requirement, and second, the nitrogen equilibrium. The caloric requirement may be readily ascertained according to the height-weight formula of Du Bois and Du Bois.[3] Food administered in accordance with this standard[4] should satisfy all theoretic demands. The nitrogen equilibrium represents the lowest possible diet which could be exacted of any patient. Food, under these circumstances, results in the conservation of the protein tissues, but does not necessarily prevent the loss of fat. This principle has been applied in the treatment of obesity; it was successfully used in the prolonged dietetic experiments of Chittenden on normal people, and is employed here. No living being can afford to lose muscle and glandular tissue indefinitely. How far the fat store of any individual may be depleted with advantage is another question. There is much to be said in favor of allowing the diabetic to become thin, so that his metabolism may be established at a lower level, as has so frequently been urged, but it should be distinctly appreciated that this loss of weight should occur in the fats and not in the vitally necessary proteins. It is with these ideas in mind that the nitrogen equilibrium has been chosen as the lowest possible food standard by which diabetics may be maintained in a state of physical and mental wellbeing over long periods.

The kind of food provided for the diabetic may ultimately prove to be of more importance than is accredited to it at present. That a protein-fat diet low in carbohydrate should be employed is common knowledge. The proportion of fat and protein, however, and the height to which the protein-fat foods are raised before carbohydrates are added are still open questions which are answered in widely divergent ways by different clinicians. In the present observations the diets outlined in Tables 1 and 2 were used whenever possible. These are as low in fats as it is possible to make them and yet render them palatable over long periods, and they afford the maximum variety of which a carbohydrate-free list is capable. The low fat content of these diets was insisted on as being the most satisfactory manner in which to

3. Du Bois, D., and Du Bois, E. F.: The Archives Int. Med., 1916, **17**, 863.
4. Gephart, F. C., and Du Bois, E. F.: The Archives Int. Med., 1916, **17**, 902.

TABLE 1.—DIETS OF SPECIFIED CALORIC VALUE IN WHICH THE FAT IS KEPT AT A LOW LEVEL. THE PROTEIN AND FAT ARE APPROXIMATELY EQUAL TO EACH OTHER, GRAM FOR GRAM. FROM THESE TABULATIONS, APPROXIMATE DIETS OF ANY CALORIC VALUE MAY BE READILY CALCULATED. THESE ARE THE DIETS USED IN MOST OF THE PRESENT OBSERVATIONS [5]

Food	500 Calories Gm. or C.c	1,000 Calories Gm. or C.c.	1,500 Calories Gm. or C.c.	2,000 Calories Gm. or C.c.
Breakfast:				
Eggs	(1) 50	(2) 100	(2) 100	(2) 100
Bacon*	40	50	60	
Ham	....	..	....	75
Butter	....	5	10	15
Vegetables†	....	....	....	100
Black coffee				
Dinner:				
Broth	150	150	150	160
Steak‡	40	100	140	160
Vegetables†	200	200	200	300
Cream cheese	....	....	20	30
Butter	5	10	15	20
Olive oil	....	10	15	15
Black coffee				
Supper:				
Broth	150	150	150	160
Eggs	....	....	(1) 50	(2) 100
Steak‡	40	75	100	140
Vegetables†	200	200	200	300
Butter	5	10	15	20
Tea (plain)				
Total Value of				
Protein	40.4	71.2	99.9	135.7
Fat	31.0	71.6	110.7	144.4
Carbohydrate	12.0	12.0	12.5	21.7
Calories	503	1,006	1,489	1,986

* The bacon is weighed uncooked. The fat and protein content is calculated for the cooked product.

† Two or three different vegetables should be chosen from the accompanying list (Table 2), which tabulates the vegetables containing 5 per cent. or less of carbohydrates.

‡ The caloric equivalent of other carbohydrate-free meat or fish should be frequently substituted from the accompanying list (Table 2), to furnish variety in the diet.

5. For complete details of these diets, see Jour. Med. Soc. New Jersey, 1916, **13**, 339.

TABLE 2.—List of Meats, Fish and Vegetables Allowed in the Diets of Table 1. The Meats Are Tabulated in Units Approximately the Caloric Equivalent of 10 Gm. of Beefsteak, and May Be Substituted for the Same Caloric Value of Beefsteak in Table 1

CALORIC EQUIVALENT OF 10 GM. OF STEAK IN CARBOHYDRATE-FREE MEAT OR FISH

Food	Gm.	Fat, Gm.	Protein, Gm.	Calories
Steak	10	1.0	2.4	19
Roast beef	5	1.4	1.1	18
Tongue	7	1.4	1.6	20
Lamb chop	5	1.5	1.1	18
Roast lamb	8	1.3	1.6	20
Sweetbreads	11	0.1	4.4	19
Boiled ham	7	1.4	1.5	19
Fried ham	5	1.7	1.1	20
Roast pork	9	0.9	2.6	19
Bacon	9	1.7	0.9	20
Chicken	11	1.0	2.4	19
Duck	9	1.3	1.8	19
Guinea hen	12	0.8	2.8	19
Squab	9	1.1	2.1	19
Turkey	7	1.3	2.0	20
Bluefish	13	0.6	2.5	20
Halibut	16	0.7	2.3	20
Mackerel	15	1.0	2.5	20
Sardines in oil	7	1.4	1.6	20

VEGETABLES ALLOWED ON "CARBOHYDRATE-FREE" DIET

Asparagus	Cucumbers	Lettuce	Spinach
Brussels sprouts	Eggplant	Pickles (sour)	String beans
Cabbage	Endive	Rhubarb	Swiss chard
Cauliflower	Greens	Sauerkraut	Tomatoes
Celery	Kohl-rabi	Sorrel	Watercress

control acidosis. It may be noted that the fats and proteins remain approximately equal to each other, gram for gram, throughout these diets.

The nitrogen of the food was either calculated according to Atwater and Bryant's tables,[6] or actually determined by analysis. The correspondence between the two methods was close enough to justify the use for the present purposes of the values as given in the tables. The nitrogen of the food, urine and feces were all determined by the

6. Atwater, W. O., and Bryant, A. P.: Bull. No. 28, U. S. Dept. Agric., 1906.

Kjeldahl method. Most of these patients were under strict supervision, either in a small metabolism ward or in the private rooms. Twenty-four cases were studied. Of these, only a few will be given in detail. The urinary glucose was estimated by Benedict's[7] modification of Fehling's solution, the acetone substances in the urine by Shaffer's[8] procedure, and the blood sugar by the method of Lewis and Benedict[9] or that of Bang.[10]

The number of calories of the protein-fat diet necessary to bring about nitrogen equilibrium was found to be slightly greater than, equal to, or considerably less than the total average caloric requirement of persons of the same age and sex as the diabetics. (Tables 3 and 4.)

Since it is known that "if a given subject's basal metabolism is more than 10 per cent. from the average, it may be regarded as abnormal, but cannot be proved abnormal unless the departure is at least 15 per cent.,[11] it may be concluded that the amount of food demanded to result in a nitrogen balance is not greater, in any one of the present series of cases, than the upper limits of normal metabolism, but may be lower (Table 4). This finding for diabetics is in strict accord with that of E. Voit and Korkunoff,[12] who demonstrated that under normal conditions, "if fat and meat be ingested together, the quantity of the latter necessary to establish nitrogenous equilibrium is reduced to between 1.5 to 2.1, the starvation minimum."

The case[13] detailed in Table 5 demonstrates at what a low level of metabolism a nitrogen balance may be obtained. This child was evidently an instance of "total diabetes." The D : N ratio was constantly in the neighborhood of 3.65 : 1, indicating that no carbohydrate, derived either from the small amount of ingested starch or from the protein, was utilized. Inasmuch as starch, whether preformed or derived from protein, has been considered the most efficient sparer of nitrogen, it is remarkable that in this patient nitrogen equilibrium could be effected on a diet of 19 calories per square meter per hour, which is only a fraction of the normal standard. (Boys 12 to 13 years of age on such a diet may be considered to have normal standard of metabolism of 54.9 calories per square meter per hour; Gephart and Du Bois do not give any figures for the normal basal metabolism of girls.) On calculating the metabolism for the whole period of observation it is noted that although only 0.49 gm. of nitrogen were lost per day, yet the food

7. Benedict, S. R.: Jour. Am. Med. Assn., 1911, **57,** 1193.
8. Shaffer, P. A.: Jour. Biol. Chem., 1908, **5,** 211.
9. Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, **20,** 61.
10. Bang, I.: Biochem. Ztschr., 1913, **57,** 300.
11. Gephart, F. C., and Du Bois, E. F.: THE ARCHIVES INT. MED., 1916, **17,** 906.
12. Lusk, G.: Science of Nutrition, Ed. 3, 1917, p. 254.
13. This patient was studied in the pediatric clinic under Dr. J. Howland; the blood sugar was determined by Harold L. Higgins.

TABLE 3.—Condensed Data from Cases of Diabetes Mellitus, Which Show, by Periods, the Relation of the Caloric Value of the Diet to Maintenance, as Measured by the Nitrogen Equilibrium. The Daily Caloric Value of the Food Was Approximately Constant During Each Period

Patient	Period, Days	Glycosuria, Gm. per Day	Nitrogen per Day, Gm.			Carbohydrate-Free Diet, Calories per Day*	Calories per Kilo per Day	Calories per Sq. M. per Hour
			Intake	Output, (Urine and Feces)	Balance			
	3	0	11.4	14.9	—4.5	1,006	22.2	27.8
	4	0	16.1	17.9	—1.8	1,503	33.1	41.6
Case 1	**7**	**0**	**17.9**	**16.7**	**+1.2**	**1,704**	**37.5**	**47.2†**
Med. Hist. Nos. 36800 and 37408	**9**	Trace	**22.2**	**21.6**	**+0.6**	**2,003**	**44.1**	**55.4**
Man, aged 38				Two	months	later		
Height, 5 ft. 7 in. (170 cm.)	9	6	15.6	16.7	—1.1	1,504	33.1	41.6
Weight, 100 lbs. (45.4 kg.)	5	0	10.7	14.8	—4.1	950	20.9	26.3
General condition, very poor	3	0	15.1	15.9	—0.8	1,473	32.4	40.8
	14	**0**	**16.5**	**17.6**	**+0.9**	**1,711**	**37.7**	**47.4**
	16	**0**	**16.9**	**17.7**	**+1.2**	**1,934**	**43.7**	**54.0**
	4	**45**	**17.6**	**16.1**	**+1.5**	**1,487**	**29.5**	**39.7**
Case 2								
Med. Hist. No. 36901	**2**	**30**	**18.4**	**17.5**	**+0.9**	**1,811**	**35.9**	**48.4**
Woman, aged 35	4	8	13.7	14.6	—0.9	1,106	21.9	29.5
Height, 5 ft. 6 in. (168 cm.)	3	0	4.6	9.0	—4.4	591	11.7	15.8
Weight, 111 lbs. (50.4 kg.)	2	0	14.5	15.8	—1.3	1,182	23.5	31.6
General condition, fair	**5**	**0**	**20.0**	**14.4**	**+5.6**	**1,750**	**34.7**	**46.7**
	8	0	14.0	15.2	—1.2	1,412	28.3	36.3
Case 3								
Med. Hist. No. 37161	3	0	11.4	15.5	—4.1	988	19.8	25.4
Man, aged 43	**3**	**0**	**18.5**	**15.2**	**+3.3**	**1,700**	**34.1**	**43.7**
Height, 5 ft. 10 in. (178 cm.)	**6**	**0**	**19.4**	**17.9**	**+1.5**	**2,104**	**42.2**	**54.1**
Weight, 110 lbs. (49.9 kg.)	1	0	7.4	13.8	—6.4	500	10.0	12.9
General condition, poor	**2**	**0**	**25.8**	**18.2**	**+7.4**	**2,193**	**44.0**	**56.4**
	7	3	7.9	11.5‡	—3.6	712	11.9	18.2
Case 4								
Med. Hist. No. 36776	**4**	**0**	**13.1**	**12.9‡**	**+0.2**	**1,133**	**18.9**	**29.0**
Woman, aged 56	3	0	1.6	5.5‡	—3.9	49	0.8	1.3
Height, 5 ft. 3½ in. (161 cm.)	**2**	**0**	**11.6**	**11.4‡**	**+0.2**	**1,056**	**17.6**	**27.0**
Weight, 132 lbs. (59.9 kg.)	**11**	**0**	**15.1**	**11.9‡**	**+3.2**	**1,523**	**25.4**	**39.0**
General condition, normal								
Case 5								
Med. Hist. No. 37488								
Man, aged 26	**7**	**0**	**14.7**	**12.9**	**+1.8**	**1,470**	**25.3**	**35.9**
Height, 5 ft. 9 in. (175 cm.)	**3**	**0**	**20.0**	**14.1**	**+5.9**	**1,943**	**33.4**	**47.4**
Weight, 128 lbs. (58.1 kg.)								
General condition, fair								

* "Carbohydrate-free" diets contain approximately the proportion of proteins, fats and carbohydrates given in Table 1, with the exception of Cases 8 and 9, in which the carbohydrate content of the food was somewhat higher.

TABLE 3.—Condensed Data from Cases of Diabetes Mellitus, Which Show, by Periods, the Relation of the Caloric Value of the Diet to Maintenance, as Measured by the Nitrogen Equilibrium. The Daily Caloric Value of the Food Was Approximately Constant During Each Period.—
Continued

Patient	Period, Days	Glycosuria, Gm. per Day	Nitrogen per Day, Gm.			Carbohydrate-Free Diet, Calories per Day*	Calories per Kilo per Day	Calories per Sq. M. per Hour
			Intake	Output, (Urine and Feces)	Balance			
	4	45	12.6	15.5	—2.9	1,318	24.2	33.8
Case 6								
Med. Hist. No. 37267	3	22	10.2	14.7	—4.5	988	18.2	25.3
Man, aged 35								
Height, 5 ft. 7 in. (170 cm.)	5	0	5.4	10.9	—5.5	421	7.8	10.8
Weight, 120 lbs. (54.4 kg.)	**4**	**0**	**13.3**	**12.0**	**+1.3**	**1,009**	**20.2**	**28.2**
General condition, normal	**4**	**0**	**15.9**	**13.6**	**+2.3**	**1,405**	**26.9**	**37.5**
	8	**0**	**18.0**	**15.5**	**+2.5**	**1,728**	**31.9**	**44.3**
Case 7	6	5	15.6	23.6	—8.0	1,503	24.4	36.1
Med. Hist. No. 37261								
Man, aged 41	5	0	15.6	17.3	—1.7	1,505	24.4	36.1
Height, 5 ft. 8 in. (172 cm.)	2	0	17.0	17.1	—0.1	1,614	26.2	38.7
Weight, 136 lbs. (61.7 kg.)	3	0	18.8	23.1	—4.3	1,903	30.8	45.6
General condition, normal	**3**	**0**	**21.4**	**19.9**	**+1.5**	**2,048**	**33.2**	**49.1**
	12	0	8.2	9.9	—1.7	609	17.9	20.9
	3	**0**	**13.4**	**10.8**	**+2.6**	**1,152**	**33.9**	**39.5**
	2	Trace	12.6	16.9‡	—4.3	1,284	37.8	44.0
Case 8	5	0	7.4	10.9‡	—3.5	595	17.5	20.4
Med. Hist. Nos. 36887 and 37230	9	0	12.5	14.6	—1.1	1,157	34.0	39.6
Boy, aged 13								
Height, 4 ft. 11 in. (150 cm.)	6	0	14.9	15.3	—0.4	1,449	42.6	49.7
Weight, 75 lbs. (34.0 kg.)	5	0	15.4	15.7	—0.3	1,363	40.1	46.7
General condition, normal				Six weeks inter				
	2	0	12.9	15.2	—2.3	1,101	32.4	37.7
	6	**0**	**13.4**	**13.4**	**+2.0**	**1,568**	**44.4**	**51.7**
	1	0	8.4	9.4	—1.0	620	18.2	21.2
	7	**0**	**21.7**	**19.0**	**+2.7**	**1,888**	**49.8**	**57.8**
	1	0	5.9	13.4	—7.5	532	19.6	19.5
	8	0	8.5	9.9	—1.4	904	26.5	26.4
Case 9	7	0	7.0	8.0	—1.0	570	21.0	20.9
Med. Hist. No. 36839								
Girl, aged 12	11	Trace	8.7	9.9	—1.2	858	31.5	31.4
Height, 5 ft. 1½ in. (156 cm.)	4	0	5.2	8.5	—2.7	529	19.5	19.4
Weight, 60 lbs. (27.2 kg.)	8	0	8.6	8.8	—0.2	840	30.9	30.8
General condition, poor	2	0	4.6	9.5	—4.9	360	13.2	13.2
	11	0	8.6	9.9	—1.3	832	30.6	30.5

† The figures printed in heavy type indicate periods in which a positive nitrogen balance was obtained; the figures in lighter print indicate the periods of nitrogen loss.

‡ In these instances, the nitrogen of the feces was estimated as 10 per cent. of the nitrogen intake; the remaining figures represent actual determinations.

TABLE 4.—SUMMARY OF TABLE 3. CALORIC REQUIREMENT NECESSARY TO PRODUCE NITROGEN EQUILIBRIUM IN CASES OF DIABETES MELLITUS, AS COMPARED WITH THE NORMAL METABOLISM OF INDIVIDUALS OF THE SAME AGE AND SEX

Case	Age	Sex	General Condition	Calories per Hour per Square Meter of Body Surface			Caloric Requirements Necessary to Establish N Equilibrium as Compared with Normal Metabolism
				Highest at which N Equilibrium Was Not Obtained	Lowest at which N Equilibrium Was Obtained	Normal Metabolism*	
1, Period 1	38	M	Very poor	41.6	47.2	43.7	8 per cent. higher
Period 2				41.6	47.4	43.7	8 per cent. higher
2	35	F	Fair	31.6	39.7	40.6	Unchanged
3	43	M	Poor	36.3	43.7	43.7	Unchanged
4	56	F	Normal	18.2	27.0	36.0	25 per cent. lower
5	26	M	Fair	....	35.9	43.7	18 per cent. lower
6	35	M	Normal	33.8	28.2	43.7	28 per cent. lower
7	41	M	Normal	45.6	49.1	43.7	12 per cent. higher
8, Period 1	13	M	Normal	49.7	39.5	54.9	28 per cent. lower
Period 2				37.7	51.7	54.9	6 per cent. lower
9	12	F	Poor	36.4			

* Basal metabolism according to F. C. Gephart and E. F. Du Bois (THE ARCHIVES INT. MED., 1916, 17, 902) plus 10 per cent. to allow for the specific dynamic action of the diet.

actually utilized amounted to only 13.9 calories per kg. per day, or 12.9 calories per square meter per hour. This remarkable effect of a low, pure protein-fat diet in conserving the body's nitrogen may be the reason for the fact that this emaciated child was able to "walk around and go riding" three months later, although she was still excreting large amounts of sugar. The present case is one of the rare instances in which a maximal D: N ratio did not prove to be a sign of immediate danger or impending death. The fluctuations manifested in the D: N ratio from day to day are similar to those noted in other cases, and may be explained by irregular periods of glucose excretion and retention and not necessarily through inefficiency in the management of the case.[14]

From the clinical point of view it is extremely important to know whether or not it is possible to restore the lost body tissue; in other words, cause an assimilation of nitrogen, on these diets. The generally accepted fact is that it is difficult to cause a prolonged deposition of protein on a protein-fat diet.[15] Strictly speaking, the "carbohydrate-free" diets used in diabetes, as in the present report, contain from 10

14. Mosenthal, H. O., and Lewis, D. S.: Bull. Johns Hopkins Hosp., 1917, **28**, 187.

15. Lusk, G.: Science of Nutrition, Ed. 3, 1917, p. 255.

TABLE 5.—Data from a Case of Diabetes Mellitus; Girl, Aged 8 Years, 9 Months; Height, 4 Feet 8 Inches (142 cm.); Weight, 47 Pounds 3 Ounces (21.4 kg.). This Patient Is Suffering from Severe Diabetes Mellitus, as Shown by the Very High D:N Ratio; at the Same Time Her Caloric Requirements Necessary to Establish Nitrogen Equilibrium Are Very Low

Date	Urine					Blood Sugar, per Cent.	Food						Nitrogen Balance, Gm.*	Calories Utilized†		
	Glucose, Gm.	Acetone Bodies as B-Oxy., Gm.	N Gm.	D:N Ratio	Calories Lost as Glucose and B-Oxy.		Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, Gm.	Total Calories	Nitrogen, Gm.		Total	Per Kg.	Per Sq. M. per Hour
6/20/16	75.6	....	.....	...	280	0.49										
6/21/16	36.0	14.7	4.70	6.0	199	0.25	15.2	1.2	7.5	...	104	2.43	—2.51	0	0.0	0.0
6/22/16	41.6	19.7	8.64	2.9	243	0.25	28.3	2.1	16.5	5.5	242	4.53	—4.56	0	0.0	0.0
6/23/16	37.8	14.9	6.94	2.8	207	0.33	31.1	2.3	18.0	5.5	261	4.98	—2.46	54	2.5	2.3
6/24/16	17.8	7.9	6.50	2.7	102	....	44.0	4.0	0.0	5.5	256	7.04	—0.16	154	7.2	6.7
6/25/16	37.4	7.5	10.72	2.1	172	....	81.4	20.4	14.1	5.5	620	13.02	+1.00	448	20.9	19.5
6/26/16	26.8	5.8	7.82	1.0	105	....	70.0	28.2	19.1	5.5	666	11.20	+2.26	561	26.2	24.4
6/27/16	+5.8‡	+4.2‡	+3.74‡	1.5	+41‡	0.33	13.2	1.2	0.0	5.5	104	2.11	.....	0	0.0	0.0
6/28/16	47.4	7.7	8.51	3.6	210	0.34	48.5	15.4	19.1	5.5	316	7.76	—1.53	106	4.9	4.6
6/29/16	47.7	8.8	9.22	3.1	216	....	48.5	15.4	19.1	5.5	316	7.76	—2.24	100	4.6	4.3
6/30/16	17.7	6.7	5.11	3.4	96	0.27	13.2	1.2	0.0	5.5	104	2.11	—3.21	8	0.3	0.4
7/ 1/16	23.0	7.2	6.30	5.7	117	....	15.4	1.4	0.0	5.5	115	2.46	—4.09	0	0.0	0.0
7/ 2/16	52.9	5.7	8.13	4.1	221	....	65.1	29.7	19.1	5.5	600	10.42	+1.25	439	20.5	19.1
7/ 3/16	55.0	9.1	9.94	3.5	244	....	73.4	28.9	18.0	5.5	682	11.74	+0.63	438	20.4	19.0
7/ 4/16	64.5	13.1	10.53	4.4	298	....	93.9	43.8	18.0	5.5	905	15.02	+2.99	607	28.3	26.4
7/ 5/16	52.8	11.2	8.93	3.9	246	....	97.9	28.1	18.0	5.5	775	15.66	+5.16	529	24.7	23.0
7/ 6/16	54.2	11.5	16.55	2.1	252	....	90.5	46.3	18.0	5.5	914	14.48	—3.52	662	30.9	28.7
7/ 7/16	61.4	13.2	11.78	3.6	287	0.32	103.6	55.1	18.0	5.5	1,049	16.58	+3.14	762	35.6	33.1

* Ten per cent. of the nitrogen of the food is calculated as being excreted in the feces.
† The figures of these columns represent the total number of food calories, less the calories lost in the urine as glucose and Beta-oxybutyric acid.
‡ Urinary specimen incomplete on this day.

Summary: From June 20 to July 6, inclusive, excepting June 27:

Total food calories	7,985	Calories utilized per kilo per day	13.9
Total calories lost in urine	3,215	Calories utilized per square meter per hour	12.9
Total calories utilized	4,770	Total nitrogen lost, gm.	7.35
Calories utilized per day	298	Nitrogen lost per day, gm.	0.49

to 15 gm. of starch derived from the vegetables. It is rather problematical what effect such a small amount of carbohydrate may have. In some instances, there is no tendency for the body to assimilate nitrogen to any marked degree. This is exemplified in Case 1, Table 3. This patient showed no appreciable rise in his slight positive nitrogen balance when the diet was increased after nitrogen equilibrium had once been obtained, either in the first or second periods of study. On the other hand, some diabetics exhibit the ability to assimilate nitrogen while on "carbohydrate-free" diets. This may be noted in Table 3; Case 2 retained 28 gm. of nitrogen in 5 days; Case 4, 35 gm. in 11 days; Case 5, 29 gm. in 10 days; Case 6, 34 gm. in 16 days, and one diabetic patient of this series whose protocol is not charted, retained 49 gm. of nitrogen in 17 days. It is perfectly apparent from these data that the diabetic may often build up body protein while on a carbohydrate-free diet.

A study of Tables 3 and 4 reveals some apparent contradictions: In Cases 6 and 8, the highest caloric value of the food at which nitrogen equilibrium was not obtained is greater than the lowest value at which equilibrium was obtained. These inconsistent results are no more opposed to one another than the very varying heights of metabolism required to produce nitrogen equilibrium in the different cases (Table 4). What the specific reason for the caloric requirement is in each case is impossible to determine; it may be stated definitely, however, from the data of Case 1 (Tables 3 and 4), that these factors may have a tendency to remain constant, although in some individuals they may vary as in Cases 6 and 8.

In Case 6, Table 3, it is apparent that in the first two periods the nitrogen output is higher, with a lower nitrogen intake than it is in some of the subsequent periods. The same fact may be noted in Case 2, Table 3. In both of these patients there was a considerable glycosuria, while this slight excess of urinary nitrogen manifested itself. It may have been that the caloric loss of the urinary sugar resulted in a greater destruction of protein, or it may be that these are mild examples of the very marked protein breakdown and excessive amounts of urinary nitrogen at times found in diabetes, as in the case of Geyelin and Du Bois.[16] In either event it is certain that nitrogen equilibrium was established at a considerably lower caloric food level in Case 6 after the glycosuria had subsided. It must be distinctly recognized, however, that the glycosuria in itself, although very marked, need not result in an increased caloric demand to establish nitrogen equilibrium. This is well shown in the case detailed in Table 5.

The discrepancy in Case 8 is well explained in Table 6, which gives

16. Geyelin, H. R., and Du Bois, E. F.: Jour. Am. Med. Assn., 1916, **66**, 1532.

TABLE 6.—An Abstract from the Complete Protocol of Case 8, Table 3. Effect of a Slight "Cold" on Glycosuria Acetonuria, Blood Sugar and Nitrogen Equilibrium in a Case of Diabetes Mellitus; Boy, Aged 13

Date	Urine					Feces Nitrogen, Gm.	Output Nitrogen, Gm.	Balance Nitrogen, Gm.	Food						Blood Sugar, per Cent.	Remarks
	Volume, C.c.	Glucose	Acetone	Diacetic Acid	Nitrogen, Gm.				Nitrogen, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Total Calories	Calories per Sq. M. per Hour		
11/16/16	1,245	0	++	+	10.08	0.60	10.68	+0.15	10.83	67.7	54.3	31.3	911	31.2	0.10	
11/17/16	1,070	0	+	+	8.67	0.60	9.27	+3.74	13.01	81.3	66.6	44.2	1,134	38.9		
11/18/16	1,670	0	+	+	11.86	0.60	12.46	+0.55	13.01	81.3	66.6	44.2	1,134	38.9		
11/19/16	1,260	0	++	+	9.95	0.60	10.55	+3.50	14.05	87.8	69.6	44.2	1,188	40.7	....	Contracted slight "cold"
11/20/16	1,605	Trace	+++	++	14.58	0.60	14.88	−0.82	14.06	87.9	85.5	44.2	1,337	45.8	0.13	
11/21/16	1,640	Trace	++	+	18.04	0.80*	18.84	−7.62	11.22	70.1	82.2	43.9	1,232	42.2		
11/22/16	1,260	0	++	+	7.28	0.80*	8.08	−5.44	2.64	16.5	0.9	18.0	150	5.1		
11/23/16	900	0	++	+	9.41	0.80*	10.21	−3.43	6.78	42.4	31.0	18.1	536	18.3	....	Maximal temperature, 99.8 F.; temperature normal on all other days
11/24/16	1,435	0	++	+	11.05	0.80*	11.85	−5.26	6.59	41.2	33.6	18.0	555	19.0		
11/25/16	1,870	0	++	+	10.29	0.80*	11.09	−2.09	9.00	56.8	52.8	18.0	798	27.3		
11/26/16	2,620	0	++	+	12.31	0.91	13.22	−1.54	11.68	73.0	60.6	18.0	937	32.1		
11/27/16	2,680	0	++	+	13.40	0.91	14.31	−2.13	12.18	76.1	66.3	18.0	1,002	34.3		
11/28/16	1,840	0	+	+	10.12	0.91	11.03	−1.71	12.74	79.6	66.6	18.0	1,020	35.0		
11/29/16	2,550	0	+	0	13.77	0.91	14.68	−0.54	14.14	88.4	64.6	20.3	1,047	35.9		
11/30/16	2,030	0	+	0	13.40	0.91	14.31	−1.61	12.70	79.4	80.9	18.0	1,152	39.5		
12/ 1/16	2,360	0	++	0	13.92	0.91	14.83	−0.09	14.74	92.1	77.5	33.3	1,235	42.3	0.09	
12/ 2/16	2,300	0	++	0	13.34	0.91	14.25	−0.94	13.31	83.2	83.8	31.3	1,249	42.8		

* Nitrogen content of feces estimated, not determined.

a portion of the protocol in detail. In the first days a nitrogen balance was readily obtained on a diet of about 1,000 calories. On November 19 a definite series of changes appeared. Each one of these variations in itself might not have been worthy of attention, but taking them together they showed that many of the metabolic processes were synchronously affected. The acetone and diacetic acids increased in the urine, as shown by the qualitative tests, a trace of glucose was found in the urine, the nitrogen excretion rose considerably, the nitrogen balance became negative, and the blood sugar increased, although the diet was scarcely changed for three days. All of these phenomena were evidently brought about by a "cold in the head" of so slight a nature that the patient himself scarcely complained of it, and the body temperature only rose to 99.8 F. on one day. All these symptoms promptly rectified themselves with the disappearance of this infection of minimal intensity, except one: the power to establish nitrogen equilibrium at the former low diet level was lost and remained so when the patient was tested out again six weeks later. It is well known that nervous shocks and the severer infections play havoc with the health of diabetics. That a very slight disturbance should have such far-reaching effects is worthy of consideration in the management of these cases.

A study of Tables 3, 4 and 5 shows that the general condition of the diabetic, that is, whether his state of nourishment be normal, fair, poor or emaciated, tends to have no direct bearing on the number of calories per square meter per hour required to establish nitrogen equilibrium.

Case 9 (Tables 3 and 4) is an instance of a patient in whom nitrogen equilibrium could not be established without the appearance of glucose in the urine. The treatment in this case was to continue the inadequate diet and maintain the urine in a sugar-free condition. The result has been a slow but evidently perceptible loss of weight and strength. Case 4 (Tables 3 and 4), a woman in good circumstances, has continued on the given diet for one year, attending to her social and household duties, and has gained strength and a little weight, although her diet is a low one. In Case 5 (Tables 3 and 4), the patient has taken the low diet indicated for an interval of 6 months; during this period he has solicited contracts for an engineering company, being on his feet nearly all the time, and feels perfectly strong and well. In Case 7 (Tables 3 and 4) the patient reports that he has taken the 2,000-calory carbohydrate-free diet for a period of eight months while he has been working as a farmer, and that his health and strength are good, though he has gained no weight. These few examples may serve to indicate (they are too few to prove the claim) that a diabetic need take only sufficient calories to result in a nitrogen equilibrium in order to bring about a maintenance of health and strength.

CONCLUSIONS

Diabetic patients may be established in nitrogen equilibrium by a carbohydrate-free diet having a caloric value equal to the standard total caloric requirement. In many instances this may be accomplished at a considerably lower level of feeding. The factors which determine the dietary level at which a diabetic attains a nitrogen balance are apparently very numerous, and not fully determined; glycosuria at times, and infections, even of very slight degree, may necessitate a higher diet to bring about the desired result.

A marked assimilation of nitrogen may occur in diabetics while on a carbohydrate-free diet.

The lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium of the patient. A rough estimate for clinical purposes of what constitutes a maintenance ration for the diabetic on a carbohydrate-free diet, is from 1,500 to 2,000 calories. In adjusting the value of the diet it should be borne in mind that women and small persons generally require less food than men and larger persons.

THE DISTRIBUTION OF BILE IN CERTAIN TYPES OF JAUNDICE*

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In a previous publication from this clinic[1] it was proposed by me to examine the blood for bile in cases of jaundice, and a scheme devised to make measurements on blood, stool and urine which, when correlated with the color of the skin, might throw some light on the rôle of bile in the various types of jaundice. The work covered by this report is the examination of 395 specimens of blood plasma together with an examination of the urine and skin, and in a lesser number an examination of stool and duodenal contents, according to that scheme. The methods employed are essentially those previously described, but with the following modifications. A tintometer constructed in the laboratory is now used to measure the color of the plasma, and readings can be made more accurately than by our earlier method, by which test tubes were simply held parallel and observed down the length of the tube. The color of the plasma is taken as an index of the bilirubin content and the amount is expressed by a number corresponding to the number of times the plasma must be diluted to reduce the color to a tint that can just be discerned in a column 1 cm. deep.

I am of the same opinion as formerly expressed, that the yellow color of plasma is due solely to bilirubin, and that Gmelin's test with nitric acid can be used to test for it. To substantiate this claim I made parallel tests in 239 cases, using Gmelin's and the Huppert-Cole tests. The results were identical in 224 cases, contradicting in 15. In 3, the Huppert-Cole was positive while the nitric acid test was negative. In 12 the nitric acid test was positive and the Huppert-Cole test negative. But the value of the Huppert-Cole tests depends to a certain extent on the quantity of plasma used, and it is sometimes negative because not enough plasma is available. This slight discrepancy is certainly explainable by the difference in delicacy of the tests and does not disprove at all the identity of the substance tested for.

The test for bile salts in the blood is modified so that we may now dialyze 3 c.c. of plasma in 9 c.c. of water through collodion sacs, where

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1. Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, THE ARCHIVES INT. MED., 1917, **19**, 344.

formerly we dialyzed 5 c.c. into 10 c.c. of water and alcohol. For cholesterol in the blood I have found no satisfactory and practicable method.

Bile Pigment.—Three hundred and ninety-five specimens of blood plasma were examined in this manner. Of this number, seventy-five were described as colorless; that is, there was no distinct yellow color present, there being only a faint turbidity, or a faint pink or buff tint distinguishing the specimen from water. This group of seventy-five all gave negative results when tested chemically for bilirubin.

Two hundred and twenty-two specimens were distinctly yellow and gave a chemical test for bilirubin. The specimens of this group measured from 15 to 375. Forty represents the critical point at which the cholemia becomes a visible jaundice. Of the 222 specimens, only two were over 40 without the patient being jaundiced, and but ten were under 40 with the patient jaundiced.

Between the 75 specimens and the 222 giving a chemical test for bilirubin were 94 specimens that were distinctly yellow in color, but gave no chemical test for bilirubin. It is in this group that the possibility of the presence of some yellow substance other than bilirubin must be seriously considered. In this group was the blood from 10 primary anemia patients; from 7 patients who had been jaundiced previously; from 11 with acute infectious diseases in which jaundice is very common; and 6 with some disease of the liver or gall ducts; that is, 34, or about one third, in which bilirubin is commonly found. In some of them bilirubin had actually been found previously, and in others it was found subsequently. Inferentially, we can say that bilirubin was present in one third of all these, but in amounts too small to be detected chemically. The remaining two thirds were all from normal individuals or patients admitted to the hospital for some condition not associated with jaundice. In all this class of doubtful, subicteric plasmas, at no time was there ever present any pigment in large amounts. I have repeatedly tested those specimens for luetin and urobilin, which are supposed to pigment the plasma at times, but in this group neither of these was found. And since it is common to find bilirubin in amounts large enough to be tested chemically in perfectly normal persons, it is safe to assume that bilirubin is the pigment in this entire group of 94.

By an analysis of the 222 specimens of blood plasma that contained bilirubin in amounts large enough to give a chemical test, considerable light is thrown on the behavior of bilirubin, per se. This has aided distinctly in the interpretation of the various findings in particular groups of cases and somewhat in the interpretation of individual cases. As indicated in the foregoing, the degree of staining of the plasma

varied from 15 to 375 and 40 represents the critical point at which the cholemia becomes jaundice; 100 represents a distinct jaundice; 300 and over a marked jaundice. The series does not contain a case of that very extreme jaundice sometimes seen in prolonged, complete biliary obstruction.

One hundred and forty-one of the specimens were from jaundiced patients; 81 were from patients not jaundiced. In the group of 81 are 14 from normal patients; 20 from patients admitted for conditions in no way associated with jaundice. I frequently find blood plasma very distinctly stained with bilirubin where there is absolutely no explanation, unless it be that a relative degree of cholemia is normal. A goodly number of these cases were investigated repeatedly and the findings confirmed, but no individual or physiologic variation can be described as yet. On the other hand, the degree of cholemia was frequently found distinctly above 40, the critical point where jaundice should be expected, yet none could be observed by the ward physicians. Three were found at 50 or over.

Of the 395 examinations made, it was found in seven cases that the patient was described as jaundiced, but the plasma was found absolutely colorless. This at first suggests jaundice without cholemia, but six out of seven cases were patients with a very severe secondary anemia, in which the normal pigmentation is exaggerated by pallor, and the condition simulates jaundice; the remaining one was described as doubtful. We thus dismiss from this report jaundice without demonstrable cholemia.

I have found that a distinctly higher degree of cholemia can exist without choluria, and 60 is found to express the critical point for choluria or the average above which cholemia becomes choluria. There is, however, a wide range in the degree of cholemia without choluria, so much so that when some of the more certain factors concerned in the behavior of bilirubin in the blood are determined, this disparity may be of much diagnostic importance.

One hundred and fifty-three of 220 specimens showed a chemical test for bilirubin in the plasma without choluria. These ranged from 15 to 275. In many cases this retention of bilirubin was associated with impaired kidney function. In other cases no other retention could be demonstrated and there was no reason to expect any impairment of kidney function. The duration of the jaundice, as well as the intensity, seems to be a factor in determining this disparity. In general, a more prolonged and a more severe jaundice is associated with a high cholemia when there may be no choluria. Also, when there is disease of the liver with change in its size and consistency, this disparity is frequently marked. In diseases of the bile ducts the disparity is less

frequent and less marked. Choluria without cholemia was not seen; also choluria without jaundice, in so far as bilirubin alone is concerned, has not been observed.

From the foregoing analysis of 222 cases in which bilirubin was found chemically, I am impressed with the following points in the behavior of bilirubin in the blood; that bilirubin is very commonly present in the blood of normal individuals in varying amounts; that it is usually readily diffused through the lymph into the skin, but less readily through the kidney; that it may be fixed in the blood, and thus withheld from lymph and urine; that it is not formed or retained in the lymph in higher concentration than in the blood; that it never appears in the urine without reaching and maintaining a certain concentration in the blood.

Bile Salts.—In studying the bile salts in the blood I have thus far found no satisfactory quantitative method. Further studies on the dialysis of blood plasma through collodion into water confirms the belief that cholesterin and lecithin are not so dialyzed, and that the Pettenkofer test on the dialysate, together with the spectrum, is a specific test for bile salts. It is not yet possible to bring much order out of the chaotic findings that appear in investigating bile salts, and until a quantitative method is used and a more satisfactory method is found for the urine, very little can be said with assurance about the behavior of bile salts in the blood. A brief analysis of some of the results alone is justifiable.

Out of 395 specimens examined, bile salts were found in 124. In 87 cases bile salts occurred in the blood in conjunction with bilirubin. This occurs most commonly when bilirubin is highly concentrated in the blood and when both bile salts and bilirubin are present in the urine. In 37 cases bile salts occurred alone. This was most often in cases of primary anemia, acute infectious diseases, diseases of the liver in which there is change in the size and consistency of the liver, and in nephritis. In 10 cases bile salts were found in conditions never associated with jaundice. In 4 cases bile salts were found in normal individuals. When larger amounts of plasma are dialyzed, bile salts are very often found in normal blood, and it is my impression that if 15 c.c. of plasma are dialyzed by the method described and all the dialysate be concentrated into 2 c.c., the Pettenkofer test will be uniformly positive in normal persons. In 106 cases bile salts were found in the blood, and not in the urine; in 13 bile salts were in the urine and not in the blood. This disparity of salts between cholemia and choluria, with a very small number showing salts in the urine and none in the blood, but a large number with salts in the blood and none in the urine, suggests a process of retention; whether this is due to a

fixation in the blood or a diminished permeability of the kidney is not yet clear. More accurate methods for examining the urine and a quantitative study of the blood are necessary to clear this up.

Urobilin.—One hundred and thirty-three specimens of blood were examined for urobilin and twenty-two found positive. This rather large number was at first surprising after the consistently negative results which I have previously reported and which other observers report. The method used is the same as that used previously, namely, the plasma is centrifuged with an equal volume of 90 per cent. alcohol saturated with zinc acetate and Ehrlich's aldehyd reagent added to the clear liquid. Both the purple red color and the spectrum were found in every positive test. The positive results are attributed to the selection of the patients and the time of taking the specimens.

Of the twenty-two positive cases, in eighteen urobilin occurred in conjunction with bilirubin, and in nine cases it was found where no jaundice was observed. In three instances urobilin was found in large amounts in the plasma of patients that were not jaundiced and moreover the plasma itself was practically colorless.

The urine was examined in 325 cases and urobilin found 110 times. In eighty-eight cases there was urobilin in the urine with none in the blood. In no instance was there urobilin in the blood, with none in the urine. In but two of the patients in whom a urobilinemia was found was there any distinct impairment of the kidney. In every case in which there was urobilinemia, enormous amounts were also found in the urine. It is, therefore, quite obvious that there is no retention of urobilin in the blood. Urobilin dialyzes very promptly into water through collodion membranes and leaves a perfectly clear and colorless dialysate; it can then be found in the dialysate by the Ehrlich aldehyd reagent and the spectroscope. From the foregoing observation we can say that urobilin is frequently found in the blood in large amounts without causing jaundice; that it is very promptly yielded to the kidney, and that it does not occur in the blood unless it is formed in excessive amounts.

We have over a thousand quantitative estimates of urobilin in stool and urine according to the methods of Wilbur and Addis;[2] but I do not feel that this has contributed anything to the general information on the distribution or behavior of bile. The difficulties due to irregularities in the formation and elimination of stool, catharsis, etc., have not yet been overcome; otherwise the method is entirely successful.

In the examination of the urine the methods used are the same as previously reported. No extensive use has been made of the quanti-

2. Wilbur and Addis: THE ARCHIVES INT. MED., 1914, **13**, 235.

tative method for bilirubin, as described by Whipple.[3] Although it has worked quite satisfactorily in deeply pigmented plasmas and urines, when smaller amounts of pigment are present I have difficulty in getting readable colors.

In a previous publication by Hoover and myself,[4] dissociated jaundice was elaborated and some of its terms defined. In the present report little can be added to the general premises of that work, especially anything on the significance of dissociation itself. In considering the various groups of cases separately the dissociation begins to take some form and meaning. Practically every case of jaundice, if the urine and blood be followed carefully through the onset and disappearance of the jaundice, will present dissociation at some time or other.

Laennec's Cirrhosis.—I have observed 18 cases of Laennec's cirrhosis with alteration in size and consistency of the liver, chiefly the small contracted liver. Some of the patients had ascites. Thirty-seven observations were made; bilirubinemia was found in 31 instances, and in all the 31 cases there was jaundice. The bilirubinemia varied from 20 to 350. Bilirubin was found in the urine of 17 patients, but there was a marked disparity between cholemia and choluria; six plasmas were found at 60 or over without choluria; bilirubin was not withheld from the lymph, but was not always freely yielded to the kidney. In none of these cases was there any great impairment of kidney function, so the bilirubin is probably fixed to the plasma. In the cases in which the jaundice had been the most prolonged this fixation was most marked; the severity of the systemic symptoms was never an index to the fixation. Bile salts were found in the blood in 10 cases; in the urine in 12. There seems to be no retention of the salts in the blood.

There is in this group a very common and mystifying dissociation of the biliary elements in both blood and urine, from which the observer has gathered nothing but confusion. In two cases there was at one time a marked increase in the bile output found in the stool, associated with a marked jaundice and deep choluria, showing that the formation of bile pigment had been increased. In three cases there was a vary marked diminution of the output of bile in the stool simultaneously with a want of bile in the urine and a very moderate jaundice, showing a definite diminution of the formation of bile. In five there was a distinct diminution of bile in the stool at a time when the blood, urine and skin were deeply stained, thus showing that obstruction to the drainage of bile sometimes occurs. Several cases

3. Hooper and Whipple: Am. Jour. Physiol., 1916, **40,** 332.

4. Hoover, C. F., and Blankenhorn, M. A.: Dissociated Jaundice, THE ARCHIVES INT. MED., 1916, **18,** 289.

went through a period of jaundice and ascites without showing any demonstrable change in the daily output of bile in the stool.

Hanot's Cirrhosis.—Three cases of Hanot's cirrhosis were examined, but very little disturbance in the formation or distribution of bile could be found; a thing quite surprising considering the alteration in the size and consistency of the liver and the general symptoms. The same can be said of three cases of syphilitic disease of the liver, except of one in which there was great deformity about the hilus of the liver, as shown at necropsy, with obstruction of the ducts.

Obstructive Jaundice.—Nineteen cases of obstruction of the bile ducts were observed and twenty-three specimens of blood taken. Twenty-three specimens contained bilirubin, most of them over 100. All were jaundiced, and all except two were accompanied by bilirubin in the urine. In this group there is very little disparity between cholemia and choluria, but inasmuch as there is a higher average cholemia than in the cirrhosis group, that point in difference is of little value. In twelve out of twenty-three plasmas, bile salts also were found. In the urine, too, bile salts and bilirubin were very seldom dissociated in this group. This consistency between bile pigment and bile salts in both blood and urine in obstructive jaundice, especially at the onset, or while the process is progressing, is regarded by me as characteristic of obstructive lesions. Very few exceptions to this have been found that cannot be explained by some complication, such as septicemia, nephritis, etc. After the obstruction is relieved the bile salts disappear from the urine and blood first, and we then have, of course, a dissociation, but the dissociation is of renal origin. The early obstructive lesions are the best and most common examples of the so-called "complete icterus": that is, bilirubin and bile salts in both urine and blood. The stool in obstructive jaundice varies in its bile content according to the extent and duration of the obstruction. That the bilirubin content of the blood and urine must necessarily become greater as the amount in the stool diminishes is not true. I observed three cases in which the stools were acholic for over a week, during which time the jaundice remained the same, and the same amount of bilirubin was given off each day by the urine; apparently the formation of bile had been diminished by the obstruction to an amount that could be eliminated by the kidney as fast as it was formed. In all three cases there was no way of estimating the condition of the portal blood flow, so that it is not certain that biliary obstruction alone was the inhibiting factor.

One case has been observed, including a necropsy, in which no lesion save obstruction could be found, yet the patient went six days with only a very slight increase in the cholemia and jaundice. I am

of the opinion that under some circumstances obstruction alone will inhibit the formation of bile.

Sixteen cases were investigated in which a diagnosis of cholelithiasis was made, but in which no obstruction could be proved. Seven of the plasmas contained bilirubin and three bile salts, and that only in very small amounts. None of the patients was jaundiced and none had bile in the urine (either pigment or salts). Seven of these patients were operated on, and in three gallstones were found; but of the three only one showed cholemia before the operation, while of the four who had no gallstones at operation, three had shown cholemia before the operation. The examination of the blood for small amounts of bile has thus far been of no aid in the diagnosis of gallstones that are producing no obstruction.

Catarrhal Jaundice.—Seven cases of catarrhal jaundice were examined and nine specimens of blood taken. Bilirubin was found in all; bile salts in four. The distribution and behavior of the bile resembled obstructive jaundice in this respect: there was little dissociation of the pigments and salts in both blood and urine except after the process began to subside. There was also an intestinal hypocholia. Unlike most obstructive lesions, there was frequently urobilin in the urine.

Chronic Passive Congestion.—Twelve cases of heart disease with chronic passive congestion of the liver were examined; most of them while decompensated. Bilirubin was present in ten cases; bile salts in three. Only small amounts of bilirubin were found, and but two of the patients were jaundiced, and only one had bile in the urine. There was considerable dissociation in the blood. Like Hanot's cirrhosis, there is little change in the distribution of the bile pigment in proportion to liver changes.

Septicemia.—Thirteen patients with septicemia were investigated, including 3 cases of typhoid, 5 of streptococcus and 4 of colon infections. In 10 there was bilirubin in the plasma and 5 bile salts; 6 had large amounts and were deeply jaundiced, but only 2 of the 6 had bile salts in the blood. On account of the liability to so many complications, especially nephritic, it is impossible to generalize in this small group.

Pneumonia.—Forty cases of pneumonia were investigated and 48 specimens examined. Thirty specimens contained bilirubin, averaging 50, the maximum being 100; 14 contained bile salts; 12 patients were jaundiced and 6 had bile in the urine; 19 had urobilin in the blood and 39 in the urine. It is this group that provided the large number of specimens with urobilin in the blood, but in only those cases in which the specimen was taken early in the course was the urobilin found. Urobilin was found to appear in the blood very early in the course of

the disease — in several instances preceding jaundice. It also disappears very rapidly — from the blood several days to a week before it is absent from the urine. In but four instances was urobilin found on two successive days. The severity of the infection was not an apparent factor on two successive days. The severity of the infection was not an apparent factor in the presence of urobilinemia: out of 15 patients who showed it, ten recovered.

Examination of the stool in pneumonia cases showed an increase in bile output for several days; usually during the period of urobilinemia or jaundice.

Malaria.—Five cases of malaria were examined and six specimens taken. Five out of six contained bilirubin, and none contained bile salts. The absence of bile salts is significant, but the numbers are too small to justify much speculation. The output of bile in the stool in three of this group was increased; in the other two no measurements were taken.

Ectopic Pregnancy.—Three cases of ectopic pregnancy were found and four specimens examined. Bilirubin was found in all four specimens, but only in small amounts; none of the patients was jaundiced. Bile salts were present in but one. The stools showed no increase in bile output.

Teniasis.—Three cases of *Dibothriocephalus taeniasis* were found and four specimens examined. Bilirubinemia was present in all, but only one patient was jaundiced. Bile salts were present in the plasma of two out of the three patients. In all three the stools showed an increase in bile. This group cannot be distinguished from primary anemia by the behavior and distribution of bile.

Plumbism.—Four cases of chronic lead poisoning were found and three patients had bilirubin in the plasma, but all four had bile salts in the plasma. Bilirubin was present in small amounts and none of the group of patients was jaundiced. The urine in all was negative; the stools also. The presence of bile salts in this group may be of some importance.

Primary Anemia. — Thirty-four cases of primary anemia were examined and 42 specimens taken. Thirty-two specimens of plasma contained bilirubin and 13 of the patients were jaundiced. Bilirubin was not found in the urine of any. The bilirubin in the blood in 10 specimens was 50 or over. Bile salts were found in 24 plasmas, and in 2 urines. Urobilin was found in 20 urines; the stools showed increase in bile output in all that were satisfactorily investigated. This group is characterized by a particularly high degree of cholemia without jaundice or choluria, and by a marked retention of bile salts in the blood. This is essentially the same as previously reported

Recently it has been found that in primary anemia there is a marked impairment of kidney function, and the possibility of the choluria in primary anemia being due to renal impairment must be considered. I therefore examined the plasma of 16 nephritics to determine somewhat the rôle of renal impairment in the accumulation of bile in the blood. These plasmas are uncommonly clear and colorless. Only 2 contained bilirubin; one at 5, and one at 10. This in some cases can be explained by the retention of water in the plasma. Seven specimens contained bile salts. None of the patients were jaundiced and the urine in all was negative. It is quite significant that 7 patients without apparent cause had increased amounts of bile salts in the blood, and it is very probable that the renal impairment in primary anemia is an important factor in the accumulation of the salts in the blood.

Secondary Anemia.—Seven cases of severe secondary anemia were examined. The plasma in six patients contained very small amounts of bilirubin, but none contained bile salts. Four of these patients were thought to be jaundiced, but this is explained by the great pallor. The urine of all was negative; the stools of all this group that were satisfactorily investigated showed a slight diminution of bile output. This fact is significant only when we compare this group with the primary anemias due to *Dibothriocephalus.*

The plasma of twenty-two perfectly normal persons was examined and thirty-four specimens taken. Eight specimens contained bilirubin and four bile salts. The urine in all was negative. In connection with Dr. Christie, who has examined the blood recently of many normal persons in his work on renal function, an opportunity was given me to obtain a limited number of specimens at intervals during the day, in relation to taking food and abstaining from food, but thus far the material is too limited to be of value, except that nothing radically contradictory has been found.

EXPERIMENTAL INTESTINAL OBSTRUCTION*

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REVIEW OF THE LITERATURE

The following experimental work was begun in the summer of 1915, at the suggestion of Dr. A. J. Carlson, as a further contribution toward the explanation of the cause of death in acute ileus, or high intestinal obstruction. The theories propounded to explain the fatal issue in high intestinal obstruction in man, studied comparatively in animals, are almost as diverse as the number of workers in the field. Chief among the theories that have been submitted since systematic experimentation was begun in this line may be enumerated the following:

1. *Splanchnic paresis,* or disorder of the nervous mechanism controlling the cardiac and vasomotor systems, due to irritation of the nerves in the intestinal wall.

2. *Bacterial infection,* or outward passage of bacteria through the intestinal wall; invading the peritoneum and producing a peritonitis, or invading the blood and lymphatics and producing a septicemia.

3. *Autointoxication,* or the absorption of various poisons from the intestinal tract.

This, at present the most popular general theory, embraces a diversity of modified forms, variously seeking the intoxication (1) in the stagnation of food materials and secretions; (2) in a bacterial origin; (3) in the absorption of poisonous substances elaborated by the intestinal mucosa or produced by a perversion of the intestinal secretion itself; (4) in tissue or mucosal autolysis; (5) in a disturbance of balance between the intestinal secretions; (6) in the abnormal absorption of poisons, as a result of damage to the intestinal wall.

4. *Dehydration,* or the excessive loss of water from the tissues through drainage into the intestinal lumen, followed by vomiting.

Braun and Boruttau[1] are among the most recent champions of the theory of *splanchnic paresis.* They consider the source of the trouble

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* This work was completed prior to the similar work of Dragstedt, Moorhead and Burcky, reported from the same laboratories recently in the Journal of Experimental Medicine (March, 1917, **25,** 421); but extraneous duties have unfortunately precluded the preparation of the work for publication until the present time.

1. Braun and Boruttau: Deutsch. Ztschr. f. Chir., 1908, **96,** 544.

to lie in the interference with the inherent nerve plexuses of the intestinal wall, this resulting in the stagnation of blood in the splanchnic region, in the enormous transudation of fluid into the intestine, followed by persistent vomiting, and leading finally to cerebral anemia and death. McLean and Andries[2] concur with these authorities and believe that the paralyzing effect on the sympathetic system is due to the marked overdistention caused by the gradual accumulation of gas in the lumen.

Wilkie[3] also subscribes to the hypothesis of vascular depletion, and believes that the higher mortality of acute high obstruction is due to the marked degree of vomiting in these cases, low obstruction being less fatal because of the greater reabsorption of fluid.

Hartwell and Hoguet[4] likewise recognize the rôle played by overdistention of the intestine, and particularly by the loss of water from the tissues, but do not concede sympathetic reflexes and cerebral anemia as the all important factors in the fatal outcome. Rather, they recognize the symptoms common to these cases as those characteristic of any severe sickness. At any rate, the theory of strict sympathetic nervous reflexes or intrinsic splanchnic irritation is now no longer held tenable; since in duodenal obstruction, in which there is often very little dilatation, the animals soon succumb, but survive low iliac obstruction (in which there is marked overdistention), or survive even the isolation of the intestine from its various ganglia.

Among the leading advocates of the theory of *direct bacterial infection* or septicemia we find the names of Borszeky and Genersich,[5] who base their conclusions on the finding of *B. coli* in the peritoneal cavity and blood after ligation of the colon and of the small intestine. Murphy and Vincent,[6] however, dismiss the theory as untenable, in that no peritonitis can be demonstrated in many cases of intestinal obstruction. Hartwell, Hoguet and Beekman,[4] while conceding the presence of *B. coli* in the blood from intestinal disturbances much less severe than obstruction, and the incidence of peritonitis even in intestinal obstruction without perforation, yet regard the invasion of the peritoneum most often as simply a terminal event, especially so in strangulation. Thus, cultures made immediately after death in high obstruction failed to show the slightest bacterial invasion of the peritoneum, blood, liver or spleen.

Howell,[7] however, presents the most unique defense for the theory of direct bacterial invasion. He assumes that the complex in high

2. McLean and Andries: Jour. Am. Med. Assn., 1912, **59,** 1614.
3. Wilkie, D. P. D.: Brit. Med. Jour., 1913, **2,** 1064.
4. Hartwell, Hoguet and Beekman: The Archives Int. Med., 1914, **13,** 701.
5. Borszeky and Genersich: Beitr. z. klin. Chir., 1902, **36,** 448-527.
6. Murphy and Vincent: Boston Med. and Surg. Jour., 1911, **165,** 685.
7. Howell, J.: Brit. Med. Jour., 1913, **2,** 1645.

intestinal obstruction is initiated by the increased permeability of the intestinal wall to bacteria, and that consequently the site of production of the poison and its absorption is the peritoneal cavity. The bacteria, he contends, cannot be put in evidence outside the intestinal lumen, because it is one of the functions of the peritoneum to destroy bacteria. In support of his theory, Howell cites the ease with which the migration of *B. coli* from the colon and cecum may normally occur across the body cavity, with resultant infection of the bladder, of quiescent ovarian cysts and pyosalpinx—but without producing peritonitis.

Among the various sources of autointoxication sought in explanation of the symptoms of ileus, the absorption from the intestines of the products of stagnated foodstuffs and intestinal secretions early attracted the attention of the physiologist. Bouchard was the first to emphasize this point of view, contending that the stagnation of intestinal contents resulted in the production of poisons which have a special affinity for the nervous system.

Likewise von Albeck[8] found that the products of putrefaction in strangulated loops were highly toxic on injection, reproducing the typical symptoms of obstruction. He classified them with the group of putrefactive poisons.

In this connection, Draper[9] at the outset of his work emphasized the retention of the biliary secretions as a factor in the production of toxemia in duodenal obstruction. But later experiments have led him to abandon this theory.

Later investigations, however, have shown the rôle played by food stagnation to be negligible, inasmuch as neither preliminary starving of the animal, nor thorough irrigation of the isolated loop results in any marked prolongation of life.

Among the most noted earlier investigators to seek the autointoxication in a *bacterial source* are Clairmont and Ranzi,[10] who produced low, simple obstruction in dogs and cats. They found that the injection of the filtered contents, as well as the injections of cultures grown from the intestinal contents, always produced the typical symptoms of ileus.

Later McClure[11] and Macallum repeated the work by means of simple ligation or by isolation of loops at various levels, carefully eliminating stagnant food and intestinal secretions as possible factors. The loops became greatly distended and incubated enormous numbers of bacteria, death usually supervening in a few days, often independently of perforation and peritonitis. Injection of the filtered contents of the

8. Von Albeck: Arch. f. klin. Chir., 1901, **65** 569.
9. Draper-Maury, J. W.: Am. Jour. Med. Sc., 1909, **137,** 725; *Ibid.,* Jour. Am. Med. Assn., 1910, **54,** 5.
10. Clairmont and Ranzi: Arch. f. klin. Chir., 1904, **73,** 696.
11. McClure, R. D.: Jour. Am. Med. Assn., 1907, **49,** 1003.

loop into the peritoneal cavity of normal dogs reproduced the typical symptoms of ileus but did not cause death. These experimenters ascribed the symptoms to the absorption of bacterial poisons, the loops being impermeable to the bacteria.

Murphy and Brooks[12] are the most recent and well known advocates of the theory that death after intestinal obstruction is the result of a bacterial toxemia, independent of peritonitis or septicemia. They are chiefly distinguished for the additional modification that the factors which make absorption possible are more important than the factors which produce the toxin. The toxic substance, therefore, is assumed to pass only through abnormal mucous membrane. The chief factor permitting this abnormal absorption consists of an interference with the circulation of the obstructed intestine. Thus, believe they, it is the marked secretory activity of the duodenum and jejunum, with the resultant rapid distention and circulatory disturbance, which results in earlier and severer symptoms than similar obstruction in the ileum. The symptoms and pathologic lesions following administration of such loop contents are found to be identical with those following injection of certain ptomain poisons.

The chief arguments advanced against the bacterial theory of intoxication are based on the fact that the onset of the symptoms in high intestinal obstruction is too rapid for a bacterial toxemia; and that high obstruction is more severe and fatal than low, although a much scantier bacterial flora is found in the high intestine.

Chief among the opponents of the theory of bacterial intoxication are Whipple, Stone and Bernheim,[13] who contend that the production of the toxin is due to a *perversion in the activity of the secreting mucosa* of the duodenal or high intestinal loops, this taking place even in the absence of demonstrable changes in the mucosa.

Roger[14] had already referred the source of the toxin to the activity of the intestine itself, and demonstrated the presence of a proteose in the occluded loops; but claimed that the products of the normal, unobstructed intestine were more toxic on injection than of the obstructed. Davis[15] similarly has found that products of washed out, apparently normal draining loops produce the symptoms of ileus on injection. This leads him to ascribe an excretory function to the intestinal mucosa as the source of the toxic substance.

Whipple,[16] however, finds that preparations of the normal intestinal mucosa are without marked toxic effects on injection. He holds that

12. Murphy and Brooks: The Archives Int. Med., 1915, **15,** 392.
13. Whipple, Stone and Bernheim: Jour. Exper. Med., 1913, **17,** 286.
14. Roger and Garnier: Presse méd., 1906, **14,** 325.
15. Davis, D. M.: Bull. Johns Hopkins Hosp., 1914, **25,** 33.
16. Stone, Bernheim and Whipple: Ann. Surg., 1914, **59,** 714.

the chief source of the elaboration and absorption of the poison is in the mucosa, and not the lumen, citing in chief support the fact that even dogs with draining loops may die, or if surviving, develop an immunity to the toxin; and that loop products on injection are fatal when the mucosa has remained intact, but are innocuous when the mucosa has been destroyed by sodium fluorid.

Gurd,[17] while endorsing Whipple's position as to the active rôle of the duodenal mucosa, contends that the substance responsible for the toxic symptoms is a result of *tissue autolysis*. His experiments indicate that even autolyzed normal mucosa is just as toxic as preparations of loop mucosa, thus controverting Whipple's results.

More recent investigations into the nature of the toxic substance would seem strongly to support Whipple's point of view. Thus the observations of Peterson, Jobling and Eggstein[18] on the serum changes that develop during acute experimental pancreatitis indicated that the shock and death are due to an intoxication from absorbed protein split products. Whipple, Rodenbaugh and Kilgore,[19] by similar observations, have put in evidence the same increase in noncoagulable blood nitrogen in acute intestinal obstruction, and point out that the injection of pure proteose will reproduce the same blood changes as intestinal obstruction. Whipple[20] claims that bacterial activity is not necessary for the formation of this toxic proteose, which is precipitable from loop preparations by the addition of five volumes of 95 per cent. alcohol.

Chief among the defenders of a purely physiologic cause of the intoxication, as opposed to a pathologic or bacterial, is Draper,[9] who believes, as Vidal[21] had formerly contended, that the symptoms are referable to a *disturbance in the balance between the secretions* of the duodenum and jejunum. He found that obstructions within a limit of 35 cm. from the pylorus were always incompatible with life, and refers death to the retention of some toxic secretion, probably pancreatic, which normally would be detoxified lower down by protective jejunal or ileal antiferments.

Matthews[22] by a somewhat similar series of experiments, in which he eliminates all pancreatic and gastric secretions as well as biliary, was led to arrive at a parallel conclusion, as to the necessity of a mutual interaction between the secretions of the duodenum and jejunum. His experiments seemed to indicate that the retention even of a small patch

17. Gurd, F. B.: Jour. Infect. Dis., 1914, **15,** 124.
18. Peterson, Jobling and Eggstein: Jour. Exper. Med., 1916, **23,** 491.
19. Whipple, Rodenbaugh and Kilgore: Jour. Exper. Med., 1916, **23,** 123.
20. Whipple, G. H.: Jour. Am. Med. Assn., 1916, **67,** 15.
21. Vidal, E.: Rev. de chir., 1900, **22,** 521.
22. Matthews, S. A.: Jour. Am. Med. Assn., 1910, **55,** 293.

of the duodenum, transplanted into the jejunum, was sufficient to prolong life in cases of obstruction.

Draper,[23] moreover, applied his hypothesis to feeding experiments, and seemed to get a prolongation of life in his dogs by feeding supposed neutralizing preparations of jejunal and ileac cells from normal animals. More recent experiments,[24] however, have failed to put in evidence any appreciable prolongation of life. He points out, however, the significant relation between the digestive power of the different parts of the alimentary tract and the toxicity or acuteness of symptoms following obstruction, symptoms thus being less marked in the regions of the esophagus and colon.

Recently Sweet, Peet and Hendrix[25] have reaffirmed Draper's point of view, pointing out in support the close analogy between pancreatitis and high duodenal obstruction. They concur with Whipple in conceding the presence of a toxic proteose, but claim, however, that this can arise only in the duodenum from pancreatic or gastric digestion, and never in the jejunum, which secretes only erepsin.

Hartwell and Hoguet[26] take issue with the foregoing authorities and oppose the views that the absorption of a toxin can occur in *uncomplicated* intestinal obstruction, claiming that the symptoms are always due to the *presence* of *lesions* which favor the *abnormal absorption* of toxins normally present, or that have resulted from stagnation. They believe these lesions are produced by the irritating effect of retained secretions or by disturbance in the circulation such as follows local strangulation (on inversion of the cut ends of loops), or follows overdistention from retained secretions.

They object further to Whipple's interpretation of the symptoms on the ground that the symptoms following the injection of loop contents are different from those following their assumed absorption; that, moreover, substances which on injection are toxic may actually be harmless on absorption; and that the permeability of the intestinal mucosa in uncomplicated obstruction is actually diminished, as determined by the absorption rates for strychnin and potassium iodid.

These authors[4] propose, therefore, as an alternative hypothesis, that death in *uncomplicated* intestinal obstruction is always due to *dehydration* of the *tissues*, as a result of the transudation of fluids into the intestinal lumen, followed by vomiting. In confirmation, they point out that life in such cases may be indefinitely prolonged by restoring the fluids through the subcutaneous injection of normal salt solution.

23. Draper, J. W.: Jour. Am. Med. Assn., 1914, **63,** 1079
24. Draper, J. W.: Jour. Am. Med. Assn., 1916, **67,** 1080.
25. Sweet, Peet and Hendrix: Ann. Surg., 1916, **63,** 720.
26. Hartwell and Hoguet: Am. Jour. Med. Sc., 1912, **143,** 357.

McLean and Andries,[2] as previously indicated, also believe the symptoms to be directly referable to depletion of the lymph and vascular systems, but believe death to be consequent, secondarily, on disturbance of the cerebral circulation.

Whipple,[13] however, disposes of Hartwell's objection, in the assertion that absorption of the toxin may occur in uncomplicated obstruction with a normal, intact mucosa. He explains the loss of fluid as a symptom common to any intoxication, and believes hypodermoclysis effective in prolonging life simply because it promotes diuresis. Moreover, Bunting and Jones,[27] who concur with Whipple's point of view, have found from experiments on rabbits that loss of fluid by vomiting is only a terminal event, and that, furthermore, the secretion of fluid into the duodenal loop is quite negligible. Finally, it has been found that the decrease in water content of the tissues is not alarmingly excessive in these cases, amounting to only one tenth of the body weight; or the equivalent of that produced simply by seven days of fasting, or four days of salivation through pilocarpin.

Finally, of great, perhaps decisive, importance in this connection, is the work of Dragstedt, Moorhead and Burchy,[28] recently reported. The distinctive merit of these workers lies in their success in securing complete sterilization of the isolated loops by washing with ether. The closure of such loops was found compatible with life for indefinite periods, even when involving great distention and marked necrosis, and when completed by ligation of all the blood vessels to the loop. Their findings would seem to indicate two distinct but complementary factors in the toxemia: first, the presence of bacteria, of whatever nature; second, the presence of necrotic tissue, as a substrate for the elaboration of the fatal toxins through the action of these bacteria.

Definition.—Ileus is defined, clinically, as a complex of symptoms consisting in pain, tympanites, vomiting, and inability to get a bowel movement. In experimental ileus, however, owing to the experimenter's control of conditions, any or all of these symptoms may be practically absent. Indeed, it would seem that even obstruction may be absent, as in the experiments of Whipple,[16] where well drained, isolated segments of the intestine were incompatible with life. All forms of ileus, however, are characterized by an acute toxemia. So that ileus might be defined comprehensively, therefore, as a disturbance in the functional or anatomic integrity of the intestinal tract, associated with a profound intoxication.

Working Theory.—Now this intoxication, of whatever origin, whether due to increased permeability and so increased absorption, to

27. Bunting and Jones: Jour. Exper. Med., 1913, **17,** 192.
28. Dragstedt, Moorhead and Burchy: Jour. Exper. Med., 1917, **25,** 421.

dehydration, to tissue autolysis, or to perversion of secretion, is sufficiently explained initially on the basis of the infection theory, it would seem, if it can be shown only that the presence of bacteria is necessary to initiate the sequence of changes that lead to the final absorption of a poison, or to both its production and absorption. The present experimenters have tentatively accepted this point of view as a working theory, believing that the solution of the problem resolves itself into a task of eliminating all bacteria as a possible factor in the change.

Methods.—Obstruction was uniformly and consistently produced by completely isolating about 20 cm. of the first part of the jejunum, the continuity of the intestinal tract then being restored by direct end-to-end union or by lateral anastomosis. This permits free feeding of the animal, and so reduces to a minimum starvation and loss of fluid as essential factors in the production of symptoms. It also permits the normal free drainage of the biliary and pancreatic secretions, precluding the formation of a blind pouch in the duodenum, which Sweet[25] claims is of itself sufficient to produce symptoms of obstruction.

As a part of the routine, a preliminary period of starvation was given the animal, the stomach and bowels being completely evacuated finally by means of apomorphin. To further minimize the bacterial flora, thorough washing of the loop with sterile normal saline was usually done after section. The loops were then completely obstructed by inverting and suturing over the ends, or only partially by closing one end and permitting free drainage from the other.

Symptoms.—The development of symptoms in our dogs paralleled closely those observed by other writers. During the first day and a half, after the immediate postoperative effects have worn off, the animal is fairly alert and lively, drinks water eagerly and even partakes of a little milk. A considerable amount of vomiting is evident from the outset, however, especially after drinking, the vomitus being bile tinged. Toward the end of the second day the animal becomes pinched and sick in appearance, dull and apathetic, refusing food, and manifesting a disposition to lie quiet or sit in an immobile position. If there is a tendency to movement, the animal's gait is stiff and uncertain, due to marked lack of flexibility of the muscles. A conspicuous shivering or tremor of the muscles then supervenes, and the animal almost invariably passes away at the end of seventy-two hours, with all the symptoms of profound shock.

Contrary to the observations of a few workers, most of our dogs gave no evidence of marked colic or pain, nor presented any marked abdominal distention, the abdomen, indeed, being generally scaphoid in contour. Nor were tonic or clonic spasms in evidence as a terminal event

An objection of Hartwell's[4] is pertinent in this connection, namely, that the symptoms arising from the injection of loop contents are not necessarily the same as those arising from its assumed absorption in the loop. Thus, Kukula, Clairmont and Ranzi, and von Albeck have found in general that injections of filtered loop contents produce symptoms of violent vomiting and diarrhea, quickening of the respiration, and tonic and clonic spasms. Though we have not done extensive experimenting along this line, these symptoms seemed to simulate more closely those of anaphylactic shock than of septic absorption. Thus, in one instance, intravenous injection of 6 c.c. of the centrifuged supernatant fluid produced violent vomiting of almost pure bile, purging and tenesmus, general restlessness and tendency to scratch the nose, violent tonic and clonic spasms, and finally complete collapse and death—all within fifteen minutes after injection. Though the pathologic findings are somewhat similar, namely, a marked hemorrhagic enteritis of duodenum and jejunum, yet the symptoms certainly do not closely resemble those due to complete obstruction.

Pathology.—Necropsy invariably revealed evidence of marked splanchnic congestion, especially in the duodenum and jejunum, associated with the presence usually of a mucopasty brown material in the lumen. The stomach was usually congested to a less marked degree, and contained frequently a light bile or blood-tinged fluid. The spleen and liver were swollen and congested and the kidneys at least gave evidence of cloudy swelling. The loop itself was usually greatly distended, markedly reddened and the walls swollen. The mucosa of the loop was usually much necrosed and invariably ulcerated, usually in the most dependent part, opposite the mesentery. The contents, which often had partially escaped through the ulcer into the peritoneal cavity, consisted of a characteristic thick, blood tinged brown fluid. This on microscopic examination revealed enormous numbers of bacteria. The peritoneum was usually mildly or acutely inflamed, the body cavity sometimes containing a thin, reddish, inflammatory transudate or the escaped contents of the loop.

The Rôle of Peritonitis.—The typical picture of ileus is, therefore, usually somewhat complicated by a terminal peritonitis, death being precipitated perhaps by the sudden outpouring of virulent toxins from the ruptured loop. Indeed, some investigators, such as Wilkie,[3] have never found death uncomplicated by perforative peritonitis, and Sweet[25] believes that overdistention and rupture are always the actual causes of death. Experiment 2 represents a typical case.

EXPERIMENT 2.—Operated on July 5, 1915, 8 a. m. Weight, 6 kg. Sex, female (black and white).

Operation.—Isolated about 20 cm. of intestine just below duodenum; ends inverted and sutured over; lateral anastomosis made between duodenum and jejunum; loop not washed.

July 6, 1915: Dog is active; walking around; drinks water; vomits yellowish fluid; had slight tremors in the morning.

July 7, 1915: Dog looks sick; averse to drinking; vomits bile-stained fluid. Dog in profound shock, but still alive at 9:30 p. m.

July 8, 1915: Found dead in morning; brownish fluid oozing from dog's mouth.

Necropsy.—Weight, 5.225 kg. Suture line of anastomosis in good condition; lungs edematous; liver enlarged and congested; kidneys, cloudy swelling; spleen congested; stomach hyperemic; duodenum markedly congested; jejunum congested, but to lesser degree, isolated loop dilated, thickened, and greatly reddened; ulcers, with perforation in several places; peritoneal cavity contains a large quantity of brownish fluid having a foul odor. The peritoneum is acutely congested.

Here, however, it will be seen that, though the animal died from a terminal peritonitis, the onset of the symptoms was too rapid to explain initially on the basis of peritonitis.

To eliminate peritonitis as a complicating factor and so to secure an unadultered picture of ileus, we conceived the plan of placing the closed loop extraperitoneally immediately beneath the skin, leaving an opening in the peritoneum and fascia just large enough to admit the mesentery without strangulation of the vessels. Experiment 15 is typical of the results, and shows that toxemia develops even with a peritoneum thus protected, and that the symptoms are relieved rather than aggravated when the loop perforates and free drainage obtains, even into the subcutaneous tissues. These loops, though markedly distended and congested, assume their initial condition, exhibiting active peristalsis and secreting a clear fluid.

EXPERIMENT 15.—Aug. 6, 1915, 8 a. m. Weight, 4.760 kg. Sex, female; black and tan; starved eighteen hours.

Operation.—Twelve cm. jejunum resected and ends closed (without previous washing); continuity of intestinal canal restored by an end-to-end anastomosis and loop placed extraperitoneally under skin, without drainage.

Aug. 7, 1915: Dog fairly active and takes food; marked distention of loop under skin.

Aug. 8, 1915: Dog looks sick and dull; refuses; still a marked distention of loop under skin.

Aug. 9, 1915: Dog active; eating meat; loop collapsed under skin, contents evidently having been absorbed, as there is no exudation through suture.

Aug. 10, 1915: Active; eating meat greedily; loop still collapsed, and no ill effects apparent.

Aug. 11, 1915: Active; eating meat; loop collapsed, but a serosanguineous fluid now apparent oozing from the suture. An opening was made for drainage and a part of intestinal loop exposed; the loop appears normal in color.

Aug. 14, 1915: Loop has been draining a clear serous fluid; dog discarded as he exhibited no further symptoms of interest.

In a similar manner, aspiration of the contents of a closed loop leads to a subsidence of the symptoms after their onset. This is accomplished by suturing the loop to the abdominal wall, leaving an opening in the abdomen just large enough to make the loop accessible for aspi-

ration. Thus, while aspiration in the following experiment (11) did not prevent death, which was due to other complications, yet it prevented the development of acute symptom and prolonged life far beyond the average period.

EXPERIMENT 11.—July 27, 1915, 10:30 a. m. Weight, 3.520 kg. Sex, female; pup; black and white; starved forty-eight hours.

Operation.—Twenty cm. jejunum isolated, washed with sterile, normal saline and ends inverted; end-to-end anastomosis made and loop sutured into opening in abdominal wall for purpose of aspiration.

July 28, 1915: Comparatively active; drinks water eagerly; wound of good appearance; small quantity of green vomitus in cage.

July 29, 1915: Not very active; dull; refuses milk; 4 p. m. about 50 c.c. of serosanguineous fluid containing a caseous brown sediment aspirated from loop.

Injection experiment: 3 c.c. of centrifuged supernatant fluid injected intravenously into both a collie and a bulldog, each weighing approximately 8 kg.; no pronounced toxic effects, excepting defecation and vomiting, developing a few minutes after injection. Dog soon recovered.

July 30, 1915, 10 a. m.: About 75 c.c. of fluid again aspirated from loop, this time being clear, serous in character. Symptoms are no worse, but dog still refuses food; a trace of distemper, the eyes and nostrils containing pus.

July 31, 1915: Dog found dead. Postmortem revealed that suture line of anastomosis had perforated, causing fatal peritonitis; loop, however, not perforated and of normal appearance, but contains a large amount of pasty brown substance.

Weight, 2.860 kg.

This is confirmed, further, by the development of toxemia when freely draining loops are closed, as in Experiment 43 following, in which the symptoms began to subside as drainage was reestablished by partial leakage around the tube, and ceased altogether when the clamped tube was pulled out. An analogous case is seen in Experiment 61, in which the draining loop accidentally became closed and caused death, necropsy revealing a normal peritoneum.

Obstruction by postoperative intussusception occurred in a few of our dogs, by a curious coincidence in the neighborhood of the resection, this resulting perhaps from operative trauma. While the necropsy in these cases revealed the usual findings of ileus, the peritoneum presented a normal appearance, as in Experiment 20.

EXPERIMENT 20.—Aug. 16, 1915, 1 p. m. Weight, 5.560 kg. Sex, female; brindle bull; starved forty-eight hours.

Operation.—Twenty cm. of jejunum isolated, washed with normal salt solution, end-to-end anastomosis made and isolated loop left with both ends open to drain into the peritoneal cavity.

August 17: Dog is active.

August 18: Very active; takes milk.

August 19: Fairly good condition, but less active.

August 20: 8 a. m., very dull and inactive; refuses to eat; 5 p. m., found dead.

Necropsy.—Liver greatly congested; stomach hyperemic; peritoneum, normal; anastomosis union good but suture line hyperemic; loop collapsed and with a normal healthy appearance; one end adherent to intestines; other end

closed by omentum, a thick yellow fatlike substance exuding when end was squeezed. Jejunum: at distance of about 12 inches from anastomosis almost 18 inches of proximal part of jejunum had telescoped into part below; section intussuscepted greatly congested.

This would seem to confirm the observations of a majority of the experimenters that all the symptoms and pathologic findings of ileus may be present in the absence of peritonitis.

The Rôle of Washing in Loops.—As previously intimated, efforts were especially directed toward eliminating as far as possible the bacterial content of the loops, usually by washing with sterile normal saline. Usually cultures in beef broth made from sections of the mucosa before washing showed only a moderate growth, while those made afterward were usually negative. But all attempts to arrest the process were futile, since in the washed as well as in the unwashed loop the symptoms always pursued the same course, ending usually in perforative peritonitis and death of the animal.

Although this attempt at sterilization was incapable of completely arresting the process, at least it served to delay the development of symptoms and onset of death. Thus the average length of life as found for dogs with unwashed loops was 48 hours, and for washed, 72 hours. This finding parallels qualitatively that of Whipple,[18] who found in double duodenal ligation a value of 48 hours for washed loops and from 24 to 28 hours for unwashed loops.

The Rôle of Dehydration.—The loss in weight of our dog in three days averaged about 13 per cent. of the total body weight. Starvation could not be an important factor in the reduction, since the animals could retain food a part of this period. Furthermore, Hartwell[26] has found that a dog fasting two weeks loses only 29 per cent. of its body weight, receiving meanwhile saline injections. As vomiting in our dogs was negligible, and transudation or secretion into the loop inconsiderable, the loss seemed to be due to inability to maintain a balance between liquid intake and output. The average loss observed by most investigators during this period is about 10 per cent., being negligible in amount, or that resulting alone from seven days of fasting (Draper[23]).

TABLE 1.—WEIGHT LOSS DURING OBSTRUCTION EXPERIMENTS

Dog	Weight Before, Kg.	Weight After, Kg.	Life Period, Days	Loss, Per Cent.
2	3.520	2.860	4	18.7
3	7.520	6.440	3	14.8
4	7.840	6.400	4½	18.0
5	7.060	6.440	1½	9.0
6	3.440	3.200	2	7.0
7	7.780	6.700	2½	14.0
10	4.260	4.160	2	2.4
11	3.520	2.860	4	19.0
Average	.....	.....	3	13.0

The Rôle of Overdistention.—Some investigators, notably Hartwell[4] and Sweet,[25] emphasize the rôle played by overdistention and conse-

quent strangulation as a cause of death, resulting directly from secondary perforation and peritonitis. Others such as Whipple[29] and Draper[9] have found the loop to behave in various ways, death resulting even when the loops were almost completely collapsed. We have observed a similar diversity of behavior in our dogs. Thus, while typically the loop becomes tremendously overdistended and gangrenous in appearance, culminating finally in perforation and peritonitis, yet a few were found collapsed, possessing an apparently normal mucous membrane and containing only a characteristic pasty brown substance, as in Experiment 61.

Furthermore, Experiment 43 shows that even tremendous overdistention is not necessarily incompatible with life, this dog living several days and only dying from other causes.

EXPERIMENT 61.—Aug. 7, 1916, 2 p. m. Sex, female; mongrel, medium brown; starved twenty-four hours.

Operation.—Isolated 20 cm. jejunum; restored continuity by lateral anastomosis; closed one end of loop. A small rubber tube was pursestringed into the other end, and with tube, sutured into abdominal wall for drainage.

August 8: Dog fairly active; drinks water.

August 9: Dog inactive, listless, and drowsy; refuses food.

August 10: Found dead in morning.

Necropsy.—Peritoneum normal appearance; lateral anastomosis; no leak, no inflammatory findings; liver greatly congested; duodenum and jejunum markedly hyperemic, presenting the typical findings of ileus; isolated jejunal loop not distended; mucosa slightly congested, but otherwise normal; free from ulceration; lumen partly filled with a characteristic semipasty brown substance.

The Rôle of External Drainage.—Failing to secure perfect sterilization of the loop by washing with normal saline, we adopted the method (also employed by various workers in the field) of drainage to the exterior, in the hope that the loop would finally become sterile, and so permit closure without the development of toxic symptoms. Whipple[29] has found that even such dogs draining externally usually die from ileus in from three to six days, and attributes death to the absorption of a toxin or perverted secretion from the mucosa of the loop. Our dogs, however, continued to drain indefinitely without the development of toxic symptoms, death always being accounted for from other causes than ileus (as in Table 2).

The results shown in Table 2 followed despite the fact that the skin usually retracted and closed over the loop after a week or ten days, absorption taking place then not only from the mucosa, but also from the lumen through the subcutaneous tissues. Sweet,[25] however, has given a plausible explanation of Whipple's results, in that by his method of double ligation a blind pouch is formed in the duodenum,

29. Whipple, Stone and Bernheim: Jour. Exper. Med., 1914, **19**, 144.

from which toxins are absorbed, and excreted secondarily, perhaps, into the draining loop.

TABLE 2.—RESULTS OF EXPERIMENTS WITH EXTERNAL DRAINAGE

Dog	Length of Life, Days	Cause of Death
8	130	Killed for necropsy
9	4	Postoperative intussusception of jejunum
10	15	Unknown
12	30	Infection and gangrene of laparotomy wound
15	8	Discarded after this period
25	120	Killed for necropsy
26	30	Pneumonia
32	30	Pneumonia
33	105	Killed for necropsy
35	60	Killed for necropsy
38	13	Ileus, due to intussusception of isolated loop
61	3	Ileus due to accidental closure of draining loop

Our draining loops had apparently closed, but laparotomy always showed them in a collapsed state, and careful testing with sterile saline generally revealed a minute opening through which drainage could be effected (as in Experiment 25).

EXPERIMENT 25.—Aug. 24, 1915. Sex, female; brown bull pup.

Operation.—Twenty cm. jejunum isolated, one end inverted and closed, and open end anchored into opening in abdominal wall for external drainage, the mucosa being everted; end-to-end anastomosis to restore continuity of jejunum.

August 25: Dog quite active; drinks freely of milk.

August 26-31: Continues active; eats meat; loop draining well, exuding a clear serous fluid.

September 22: Dog quite active; loop has retracted from surface and skin closed over opening, the loop ceasing to drain to the exterior.

October 23: Dog continues quite normal; exploratory laparotomy performed; inner end of loop found still closed and adherent along suture line of the end-to-end anastomosis; draining end found adherent to parietal wall at site of fistula and apparently closed. Lumen of loop then inoculated with normal saline emulsion of scraping from jejunum of another dog; laparotomy wound then closed.

October 25: Dog active; external site of fistula has opened up as a result of infectious process following inoculation; now oozing a thick, yellowish material.

October 26: Active, eating heartily; fistula draining well.

November 2: Dog active; fistula gradually healing over; secretion now serous in character.

December 12: External fistula again entirely closed over.

December 28: Dog posted; loop found as before, collapsed and of normal appearance. Water injected into lumen and squeezed out through opening in laparotomy scar; so not completely closed.

The Rôle of Intraperitoneal Drainage.—In the further attempt to sterilize the isolated loop, we adopted a novel method (a method which so far had not been used by other workers, and which even we employed with a few misgivings), namely, *direct drainage into the peritoneal cavity.* The loops were isolated as usual, washed with sterile saline and then returned to the abdominal cavity for direct drainage. This was done in the hope that the few remaining bacteria in the mucosa might finally be overcome by the peritoneal fluids; and further-

more, that the process of self-inoculation so obtaining might lead to an immunity against intoxication on subsequent closure, or at least mitigate the effects of a perforative peritonitis.

To our surprise the dogs continued active and healthy, even as in the cases of external drainage, very few of the dogs developing peritonitis so long as the loop remained open. Exploratory laparotomy always showed the loop to be collapsed, in active peristalsis, and of normal appearance. The ends were always invested by folds of the omentum, through which absorption took place.

TABLE 3.—RESULTS OF EXPERIMENTS WITH DRAINAGE INTO PERITONEAL CAVITY

Dog	Length of Life, Days	Cause of Death
17	3	Peritonitis due to direct infection from loop.
18	13	Killed for examination
19	10	Peritonitis due to perforation by bone at site of anastomosis.
27	3	Peritonitis as result of direct infection from loop.
28	4	Strangulation and gangrene of jejunum, due to excessive operative manipulation.
29	2	Perforative peritonitis, following laparotomy and closure of loop after thirteen days' drainage.
30	21	Pneumonia
31	4	Perforative peritonitis, following laparotomy and closure of loop after fourteen days' drainage
34	15	Distemper
36	15	Distemper
39	4	Peritonitis, due to direct infection from loop.
41	6	Peritonitis, due to leak at line of anastomosis of jejunum
42	3	Unknown

Results on closure, however, were quite disappointing, the animal running the usual course and suddenly succumbing, after two or three days, to perforative peritonitis (Experiments 29 and 31). Apparently the loop had not drained long enough to become completely sterile. If the self-inoculation had resulted in any degree of immunity, it was certainly rendered inoperative by the sudden flooding of the peritoneal cavity with infectious material, although the development of the symptoms of ileus seems to be delayed, as in Experiment 31.

EXPERIMENT 31.—Sept. 1, 1915. Weight, 8.54 kg. Sex, male; black and white; starved twenty-four hours.

Operation.—Twenty cm. jejunum isolated; washed with sterile normal saline, and dropped back to drain into peritoneal cavity; end-to-end anastomosis.

September 2: Somewhat inactive; vomits water given.

September 3: Dog continues quite active; eats meat greedily.

October 16: Exploratory laparotomy done; loop collapsed and of normal appearance; undergoes active peristalsis; draining end invested by omentum; lumen patent and free from pus and detritus; both ends inverted and loop closed.

October 17: Dog fairly active.

October 18: Quite active, playing boisterously when let out of cage; drinks milk greedily.

October 19: Not nearly so active; refuses milk; averse to jumping up on hind legs as though involved abdominal pain; found quite droopy in the evening.

October 20: Dog found dead.

Necropsy.—Acute perforative peritonitis, peritoneum being inflamed and cavity filled with blood-tinged brown fluid; large perforation in middle of loop, in most dependent position; stained smears show enormous numbers of bacteria.

The Final Evidence from Spontaneously Closing Loops.—Since subsequent laparotomy and closure of draining loops involved more or less risk of infecting the mucosa, even if draining sterile, we improvised drainage permitting spontaneous closure in case the lop became sterile. Tubes were inserted, as in drainage of the gallbladder, pursestringed, and the ends invaginated, the tube being withdrawn in a few days. In this way we finally secured the much sought result—*a closed, isolated loop that was compatible with the life of the animal* (Experiment 43).

EXPERIMENT 43.—Nov. 20, 1915, 8 a. m. Weight, 6.120 kg. Sex, female; black and tan beagle.

Operation.—Twenty cm. jejunum resected, one end inverted and closed; a rubber tube pursestringed and invaginated in the other end, and loop with tube anchored into abdominal wall for drainage to outside.

November 20, p. m.: Animal quickly recovered from operation and now fairly active, but tube is oozing a little blood.

November 23: Dog quite active and tube still intact; now draining the characteristic thin clear fluid. Tube clamped off to retain secretion and bandaged to retain in place.

November 24: Dog looks toxic, being much less active and tending to remain in an immobile posture on haunches.

November 25: Dog still toxic, but more active than yesterday.

November 26: Dog again well and active; tube with clamp found completely pulled out; fluid now draining directly from invaginated end of loop.

December 8: Dog found dead, having been killed last night in fight with another dog.

Necropsy.—Drainage outlet in skin healed over; draining end of loop closed; loop found enormously distended, being five or six times normal size; walls of normal appearance but somewhat thinned out; lumen contains a clear serous fluid resembling normal succus entericus. Loop with contents placed in alcohol.

As evidenced by its pugnacious disposition, this animal continued quite healthy, with a loop distended five or six times the normal size. This was quite normal and its contents were inadvertently placed in alcohol, we were unfortunately prevented from examining it for the presence of bacteria. It is hard to conceive of the loop closing in the presence of infection. But whether bacteria were present or not, this solitary case at least justifies the thesis that *an animal may continue well and active with closed and overdistended isolated loops.*

(A series of twenty dogs of this kind was run in the summer of 1916, but all the animals succumbed to heat and distemper. Other experiments are pending.)

SUMMARY

Our findings may be summarized briefly as follows:

1. A majority of the dogs with isolated loops succumb to perforative peritonitis.

2. But the development of toxic symptoms and death may occur independently of peritonitis.

3. Symptoms on injection of loop contents are different from those due to absorption.

4. Washing of the loop delays the development of symptoms and onset of death.

5. Loss of body weight is not great enough to be an important factor in the process.

6. Overdistention and strangulation are not necessary factors in the development of symptoms.

7. Animals may live indefinitely with loops draining externally.

8. Animals may live indefinitely with loops draining directly into the peritoneal cavity.

9. Dogs may continue well and active with enormously distended loops that have closed spontaneously.

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